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S. M. VARIS, M. B., C. M. Edin.,

Circular Road, L u c k n o w,

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M A L A R I A.

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D E F I N I T I O N.

Malaria is a disease of parasitical origin characterised by splenic enlargement, brief febrile attacks which recur periodically, melanaemia, and a tendency in protracted cases to irregular fever and extreme anaemia.

The most characteristic malarial manifestations are intermittent or remittent fever, certain forms of disease described as "pernicious", and a chronic cachexia with enlargement of the spleen and anaemia.

E T Y M O L O G Y.

Applied originally to the miasm or poison which was supposed to produce the disease, the name "malaria" was derived from the Italian "mal' aria", and signified "bad air". It is now used to designate the disease itself - for which purpose it is more convenient than any other.

S Y N O N Y M S.

Various names have from time to time been applied to the disease under consideration, of which the following are best known:

Chills and Fever; Malarial Fever; Intermittent Fever; Fever and Ague; Paludism or Paludal Fever; Swamp or Marsh Fever; Autumnal Fever; Miasmatic Fever; Periodical Fever. Walcheren Fever, Batavian Fever, Hungarian Fever, African Fever, Panama Fever, and Chagres Fever are names derived from localities where the disease has prevailed with especial intensity; but they are only in occasional use. Finally, Remittent Fever, Bilious Remittent Fever, Haemorrhagic Remittent Fever, Congestive Fever, Dumb Ague, Black-Water Fever, Black Jaundice, etc., are special names that have been applied to certain types or manifestations of the disease.

H I S T O R Y.

There are few diseases with which our profession has been longer acquainted than with malaria: in fact; the history of this disease reaches back to the earliest period of medical science. Not only were the common forms then well known, but also, and particularly, the uncommon and the pernicious varieties of the malady.

Protagoras describes the drowsiness accompanying intermittent fever, and the tetanus which sometimes supervenes, and tells of many cases that have terminated fatally, whence it may appear that he may have been the first to observe pernicious intermittent fever (febris int, comitata). Celsus draws the distinction between quotidian, tertian, and quartan fever, and refers to the possibility of a longer intermission in these words: "Interdum etiam longiore circitu quaedam redeunt, sed it raro evenit." He also speaks of the genus "emitritaion", which he describes as a fever lasting three days, with uncommonly long paroxysms reaching into one another. (Lib. iii, cap. 3). Archigenes was the first writer who recognised the complex nature of the hemitritaea, or semi-tertian form, as consisting of a tertian and a quotidian fever combined. He also makes mention of masked intermittents, especially when appearing in the form of dysentery or diabetes. Rhazes, the Arabian, gives an account of febris subintrans. Ebu Sina saw that rare type in which the fever occurs every sixth or seventh day, and Valescus, of Taranta, refers to a fever recurring every thirtieth day (Philos. Pharmaceut. et Chirurg., Lib. v, Ed. Hartmann Beyer, Francf., 1599). Rembert Dodœus (Med. Observat. Exempl., C. 4, p. 9) describes that form of intermittent fever designated as "katochus", and Diomedes Cornarus (Com. Lips., 1899, p. 28) first noticed combinations of intermittent fever with dysentery, or rather the intermittent form of the latter affection. No considerable attention, however, was given to the study of malarial fevers until after the introduction of cinchona bark from Peru into Spain, in the year 1640, by the Viceroy del Cinchon and his body-physician, Juan del Vego; and, indeed, this event marks an epoch in the history of medicine in its revolutionising influence upon medical doctrines. This study was stimulted in part by the conflicting results following the use of the new drug, and in part by the obstinate manner in which physicians generally clung to the old theories of Galen. No truly reliable results were reached in practice until after the apothecary's clerk, Robert Talbor, or Tabor, of Cambridge (Pyretology; or a Rational Account of the Cause and Cure of Agues, etc., London, 1672), had introduced the use of ~~of~~ larger doses and more effective forms of administration (mostly macerations in wine, or the tincture, with or without opium, which preparation he sold extensively as a secret remedy for ague); and until Sydenham conceived the idea of giving the cinchona immediately after the first attack, during the intermission, for the purpose of forestalling a subsequent paroxysm. He also pointed out the differences between vernal and autumnal intermittent fevers. Besides his works, the most notable upon this subject are those of Richard Morton, Torti, Ramazzini, and Lancisi: they remain to this day the great classics on malaria, containing as they do the fundamental clinical and therapeutical facts relating to this disease. Morton and Lancisi demonstrated clearly the relation of malaria to marsh miasm. Especially complete and keen in analysis is the nosography of Torti (Therapeutice Specialis ad Febres Quasdam Perniciosas, etc., Mutinae, 1712), whose classification of the malarial fevers, particularly of the pernicious and the mixed forms, has been followed by most subsequent authors.

The doagnostic as well as the therapeutic value of the Peruvian bark was recognised,and assisted materially in the discrimination of the malarial fevers from the other so-called essential fevers.It is interesting to note the relative accuracy of diagnosis and of description of the group of malarial fevers from the latter half of the seventeenth century onwards,in contrast to the confusion which existed regarding the other essential fevers until the discrimination of the latter by the pathological studies of our own time. In the eighteenth century the military and colonial enterprises of our own country served to extend the knowledge of the geographical distribution of malaria, particularly in tropical climates - the works of Pringle and of Lind containing especially noteworthy observations on this point.But the great mass of the very extensive literature on the epidemiography of malarial diseases,which has been so industriously collected and ably analised by Hirsch (Handb.der Histor.-Geograph.Pathologie,Stuttgart,1881) is of comparatively recent date.As regards malaria,the significance of the active studies in morbid anatomy of the first half of the nineteenth century relates to the clear differentiation of typhoid fever from malaria and other fevers,rather than to the actual contributions to the pathology of malaria,although these were not lacking.The occurrence of enlarged spleens,so-called fevercakes or ague-cakes,and even the dark colour of the organs in association with malarial fevers,had been occasionally observed,- notably by Lancisi,-but it was not until the first half of the last century that the intimate relation of these alterations to malaria was definitely established. Congestion and enlargement of the spleen were emphasised by Audauard (1808,1812,1818) as the essential anatomical lesions of malarial feverBailly,in 1825,noted,in a series of autopsies on cases of pernicious malarial fever observed in Rome in 1822,the dark colour of the cortical gray matter of the brain,and the congestion of the cerebral meninges and substance.He laid especial emphasis upon the evidences of supposed inflammation of the central nervous system and of the stomach and intestines.These anatomical observations,- together with those of Nepple)1828,1835),and,to a less extent,of Maillot (1835),- were interpreted in favour of Broussaisism,which exerted such a malign influence upon professional procedure at this period. In the United States of America,valuable contributions to the pathology of malarial fevers - especially of the remittent type - were made,during the fourth decade of last century,by Stewardson (Philadelphia),Swett (New York),and Anderson and Frick(Baltimore).The first-mentioned observer demonstrated the bronzed colour of the liver in malarial fevers,and regarded this as the characteristic anatomical criterion of the disease. His observations were confirmed and extended by the other writers named.Alonzo Clark,in 1855,demonstrated that the bronzed colour of these livers is due to the presence of granules of yellow,brown,and black pigment, which he regarded as derived from the colouring matter of the red blood-corpuscles.The monumental work of Daniel Drake,on"The Principal Diseases of the Interior Valley of North America (1650,1854) contains a large

amount of valuable information, based upon personal observation and research, as to the distribution and characters of the malarial fevers in the part of the country in question indicated by the title of his work. It is interesting to note, in the light of more recent discoveries, the ingenious arguments advanced by Mitchell (On the Cryptogamous Origin of Malarious and Epidemic Fevers, 1849) in favour of the doctrine of contagium animatum. This book deserves to rank with the more frequently quoted work of Henle relating to the same line of argument. The parasitic theory of malaria was about the same time advocated in Italy by Bassi and Rasori. The latter, in a discussion with the former, writes: "There is no objection to the belief that the parasites of intermittent fever, the first generation of which is exhausted in the first periodical attack, may go on to the second generation in the same body." Farther on he adds: "The duration of the attack is equal to the life of the parasites." Heinrich Meckel was the discoverer of the malarial pigment, which he found and described, in 1848, in the blood and organs of the dead body of an insane patient. He was, however, ignorant of the relation of this pigment to malaria. The next report concerning the pigment was, in 1849, made by Virchow, who observed it in the body of a man who had suffered from chronic malaria. There soon followed the observation of Heschl, Planer, A. Clark, Tigri, Frerichs, and others, fully establishing the relation of the pigment to malaria. The source of the pigment was regarded by Meckel and Virchow as in the spleen, and this doctrine was elaborated by Frerichs. Planer was the first (1854) who saw the pigment in the fresh blood of living patients, and he suggested that the pigment may be formed in the circulating blood - a view which Arnstein (1874) and Kelsch (1875) more fully presented and advocated subsequently. There appears every reason for supposing that some of the pigmented bodies which are now recognised as parasitic organisms had been seen by earlier observers without knowledge of their true nature. Thus, Meckel noted the presence of pigment granules in colourless, hylaine bodies devoid of definite nuclei. He, and more particularly Virchow and Frerichs, observed pigment in fusiform and curved bodies in the blood, which, although interpreted as endothelial cells of splenic origin, in all probability were, at least in part, the crescentic forms of the parasite. Some of the larger pigmented spherical organisms must have been seen and mistaken for leucocytes bearing pigment granules. Confusion, however, reigned in spite of all this. Some forms of typhoid fever were held to be malarial; some authorities held that dysentery and yellow fever were results of malaria; in malarial regions complications of endemic infections with other diseases were seen where they did not exist, and new diseases were created, such as typho-malarial fever. A consequence of all this was a terrible of quinine, which was used to overcome the supposed malarial infection or complications to such an extent as to make the value of the drug a matter of serious doubt. In order to distinguish it from other infections, the attempt was made, in the latest works on malarial fever prior to the discovery of the parasite, chiefly by clinical observations, definitely to circumscribe the limits of the fever of malaria. The conviction, on the other hand, that a malarial parasite certainly existed had induced several investigators, in a short space of time and in various places to

institute researches in that direction. After many vain efforts on the part of others, the malarial parasite was discovered by Laveran in November, 1880; and this introduced a new era into our knowledge of the disease. Indeed, it has furnished an unfailing means of diagnosis of malarial affections, and materially advanced our ideas of their pathology, as well as led to a better understanding of their clinical phenomena and various types, furnished important data for prognosis, and led to improvements in remedial procedures. But his discovery was not universally acknowledged for many years: not, indeed, until after the researches made in Italy had enriched the parasitology of malarial affections in man with new data. It is to the protozoa that the parasite thus discovered belonged, and not to the class of bacteria among which had been found many of the pathogenic agents of several infectious diseases. This was the first example of a protozoic infection in animals, although phytopathology had shown that there were plant diseases caused by analogous endocellular parasites. In many animals parasites like those of human malaria were later discovered. The so-called Bacillus malariae, described in 1879 by Klebs and Tomasi-Crudelli, which for a short period had a certain vogue, chiefly with the Italian writers, never rested upon satisfactory observations which indicated that it bore any relation to malaria; and it deserves no more consideration than the palmella of Salisbury, and the other alleged organisms that prior to Laveran's discovery were from time to time described.

GEOGRAPHICAL DISTRIBUTION.

Although it is foreign to the purpose of this essay to enter upon a minute investigation of the geographical distribution of malaria, yet it may be as well to here mention the most important foci of the disease; a more complete account will be found in Hirsch (loc.cit.).

So far as Europe is concerned, one of the most famous malarial regions of Germany lies south of the Carpathian Mountains, embracing the major part of Hungary, what are called the greater and lesser Hungarian plains, Banat, Croatia, and a part of Slavonia. Not less extensive and notorious are the fevers of Dalmatia and Istria; while they prevail under a milder form in the great plain of the Danube in Lower Austria and in the marshes, as well as in the northern portion of Galicia. A second very extensive malarial region exists in the North-German flatlands: Northern Silesia, the plain of the River Mark, the Baltic coast of Prussia, Pomerania, and Meklenburg; the marsh and meadow regions of Hannover and Oldenburg; strips of the western coast of Holland and Schleswig; the lowlands of Westphalia, as well as the marshy plains of the Rhine and its tributaries, including Holland, especially its seaboard provinces of Gröningen, Friesland, North and South Holland, and the long-famed Zealand; furthermore, the northern and western provinces of

Belgium, in those of West Flanders and Antwerp in particular. Malaria is entirely unknown, or occurs only in single localities (as in Rhinegau and the Danube bottom-lands of Würtemberg and Bavaria) in the mountainous regions of Upper Austria, in Tyrol, Carinthia, Steiermark, Bohemia, and Moravia, and in the hilly countries of middle and south-western Germany. Except on the margins of some of its lakes (e.g., Lake Constance and Zürich Lake), Switzerland is also free from it. The diseaseis endemic only on the humid islands of Falster and Laaland in Denmark. In Sweden it is to be found on the coast of the Baltic, in the districts of Carlskrona, Södermanland and Gestrikland, on the banks of the River Angermann (62° 20′ N.lat., the most northerly limit of the disease in Europe), and on the shores of the three great lakes, Wetter, Maeler, and Wener. The disease is seldom or never observed in Norway, Iceland, and the Faroë Islands. It may be found in Russia in the provinces bordering on the Baltic, especially in Esthonia; also in Litthau and in Poland; furthermore, along the marshy banks of great rivers, such as the Danube, Dnieper, Dniester, Don, and Volga. on the great steppes, and on the coasts of the Caspian and Black Seas. Malaria does notappear to prevail in Scotland and Ireland; and in England it is encountered but rarely. It is endemic only on the eastern coast and in some of the lowlands of the Thames. The disease in France is confined principally to the western and southern portions of the country. It extends eastward from the mouth of the Loire as far as Tours, and in a southerly direction along the entire western coast, which abounds in swamps and meadow-lands, almost to the Pyrenees. The southern coast, as far as the mouth of the Rhone, the plain at the junction of the Saone and the Rhone, including the city of Lyons, and the Department of Puy-le-Dôme, which abounds in swamps, are all well-known malarial localities. The most noted home of the malady in Spain and Portugal is along the south-western coast, in the bottom lands of the rivers. Still it occurs, often in very malignant form, along the northern coast of Spain, in Galicia and Asturia, in the northern provinces of Portugal, and even on the uplands of Estremadura and Castile. In the marshy valleys and plains of Sardinia and Corsica, and also on the coasts it is to be encountered. The most malarious of all European countries is, beyond question, Italy. Aside from the various humid regions in northern Italy, and that belt of country including the cities of Milan, Mantua, Pavia, Nice, Venice, and Verona, the entire western coast constitutes a vast hotbed of malaria, which often extends eastwards as far as the foot of the mountains. This region begins at Leghorn, and extends through the Tuscan Maremma, the Campagna of Rome, the Pontine marshes, the malarious environs of Naples, and, with the exception of some mountainous regions, as far as the southern coast of Calabria. The entire eastern coast, on the contrary, suffers but little from the disease, the only portion affected by malaria being the states formerly in the possession of the Roman Pontiffs. The disease is endemic, over large regions and often in a very malignant form, in the Island of Sicily, the Ionian Islands, Greece and Turkey, including Bulgaria, the vicinity of Constantinople, Albania, Roumelia, Moldavia, and Wallachia.

Regarding Africa,- along its western coast, in Senegambia, on the Guinea coast, and on the banks and islands of the Gambia, the Niger and the Senegal rivers, malarial fevers flourish to an extent and with a malignity scarcely equalled anywhere else. They also prevail, although in a less virulent form, on the eastern coast, through Mozambique and Zanzibar, as far south as Delagoa Bay; on the greater part of the island of Madagascar, and on the Comoro islands of Anjouan and Mohilla. They are, furthermore, to be found in southern Nubia, at the Upper Nile Delta, at the junction of the two arms of the Nile, and especially on the banks of the Whire Nile; also in Egypt, particularly in Lower Egypt, occurring here, again, on the banks of the Nile, and in the moist regions of the delta; and also extending along the coast of the Mediterranean Sea. In Algiers malaria is very widely diffused, and very pernicious, not only on the coast, but on the oases, in the deep and damp valleys of the mountainous regions, and on the southern slopes of the Atlas range of mountains. The disease is also to be found in the interior of Africa in various suitable localities.

So far as America is concerned, it is especially in South America that malaria prevails. The coasts of Colombia and Venezuela, Guiana, the northern part of Brazil, and the coasts of Ecuador, Peru, and Chili are extensively malarious. In Central America the Atlantic coast is especially unhealthy, that on the Pacific side presenting only here and there a few circumscribed areas of malaria. The disease prevails all along the shores of the gulf of Mexico, and extends up the valley of the Mississipi and along its tributaries. Texas, a part of New Mexico, Florida, and Georgia contain malarious regions. Malaria prevails along the coasts of South Carolina, North Carolina, Virginia, and Maryland, but to a lesser degree in the central and northern parts. There is considerable malaria in southern Michigan and along the shores of the Lakes Ontario and Erie, less on the shores of Lake Huron, and scarcely any on those of Lakes Michigan and Superior. In Pennsylvania and New York there are a few centres of mild malaria. Canada is almost exempt. There is but little malaria, and that of a mild form, on the Pacific coast. The West Indian islands are very malarious, but the Bahamas least so.

Regarding India,- a very extensive and malignant malarious region is to be found in the river districts of the Indus and the Ganges, which are annually overflowed by the water of these streams. This is true of the shores of the Brahmaputra likewise, and is also particularly the case with regard to the delta of the Ganges. The disease is quite prevalent on the western coast of Hither India, while the eastern coast seems to be comparatively exempt. On the island of Ceylon, however, it prevails with a virulence worthy of the West Indies or the Guinea Coast. It is universally prevalent in Farther India, as well as on the Sunda Islands, especially in Sumatra, less so in Borneo, Java, and Celebes; also on the Molucca and Philippine Islands. Malaria prevails in China along the entire southern and south-western coast, and on the banks of the larger streams, with a severity characteristic of the very worst malarious regions. It is endemic along the entire coast of Syria; along the northern coast of Asia Minor; in Arabia, on the shores of the Red Sea and the Persian Gulf; along the

banks of the river Tigris;around the Caspian Sea in Persia,and on the elevated plain of ~~of~~ Teheran in a most malignant form. Japan has but little malaria,and that little in a mild form;and the coast of the Corean peninsula is only slightly malarious.

So far as Australia is concerned,it appears that malaria may be found on the mainland,though in a mild form.Most of the islands of Oceania are almost exempt from malaria,offering in this respect a singular contrast to the lands nearest to them which are so severely affected.There is malaria,however,on the coast of New Guinea and of the other islands comprised in the Bismark archipelago.Malaria is unknown in New Zealand and the other islands of Polynesia,as it is also in New Caledonia though marshy regions abound.It assumes a severe type sometimes on some of the smaller islands,as the New Hebrides and the Society Islands,and,strangely enough,is entirely unknown on the Sandwich Islands and the Samoan Islands,as well as in Van Diemen's Land.

E T I O D O G Y.

P A R A S I T O L O G Y.

It was in the year 1879 that A. Laveran,a surgeon in the French Army serving in the province of Constantine in Algeria,began to study the pathological anatomy of malaria,and at once directed his attention to the much discussed question of the origin of the pigment.He observed in the blood of malarial patients certain pigmented bodies different from the melaniferous leucocytes;but he was uncertain as to their nature until,on November 6,1880,he discovered that some of these pigmented bodies threw out long flagella endowed with such active lashing movements as to convince him,as they have convinced everyone who has since then seen them,that they are living parasites.Laveran published his observations in a note to the Académie de Médicine in Paris, presented November 23,1880.This was followed by the publication of several notes in 1880 and 1881,and in the latter year appeared a small monograph on the parasitic nature of the disease by the same author.He describes in these various early publications: (1) Pigmented crescentic and ovoid bodies; (2) spherical,transparent bodies,sometimes free,sometimes applied to the surface of the red blood-corpuscles,the smallest about one-sixth of the diameter of a red blood-corpuscle and containing only one or two fine pigment granules,these representing an early stage of development of (3) larger, pigmented,spherical bodies averaging 6 mm.in diameter, but sometimes larger than a red blood-corpuscle,and containing numerous,often moving,pigment granules;(4) bodies similar to the last mentioned,but beset with active motile flagella;(5) free motile flagella;and (6) swollen spherical or deformed bodies,8 - 10 mm.in diameter,containing pigment,and regarded as cadaveric forms of the spherical parasites.Laveran noted amoebic movements of the spherical forms,grouping of the small spherical bodies together,and the occurrence of small,colourless,motile bodies,without specific characters,which

he suggested may represent perhaps the first phase of development of the parasitic elements.He regarded all of the forms as different stages of development of the same species of organism,and considered the free flagella,which he believed were formed within the spherical bodies and escaped by rupture of the envelo-ping membrane,as the perfect stage of development of the parasite and the most characteristic of the same. To his colleague Richard,stationedin Philippeville, Algiers,Laveran communicated his results.Richard,in February,1882,published a communication confirming Laveran's observations and adding certain points of importance.He described the development of the para-site from small,perfectly transparent bodies contained in the otherwise normal red blood-corpuscles.This clear body grows larger,forms pigment out of the haemoglobin of the enveloping red corpuscle,which thereby becomes gradually decolourised and reduced to a mere colour-less shell-like rim,which finally rputures and sets free the parasite.This now generally accepted view as to the intracorpuscular development of the parasite, which was first announced by Richard,was,however,in the following year abandoned by him in favour of Lav-eran's view that the parasites develop either free in the plasma or in close attachment to the surface of red corpuscles or in depressed spots on the surface. Richard observed spherical bodies with a central block of black pigment from which deliacte lines radiated so as to produce radiate forms,and noted amoeboid move-ments of the parasites. The first-mentioned observer (Laveran) continued to publish brief communications in 1882 and 1883,and in 1884 he published a larger work (Traité des Fièvres Palustres,Paris,1884) presenting his observations and views in detail.In this work he describes more fully the forms already mentioned,and he notes the occurrence of segmented forms,which, however,he did not interpret as forms of reproduction, but as forms of degeneration.It is a noteworthy fact that the observations of Laveran and of Richard were made by microscopical examination of the fresh blood. In 1883 and 1884,Marchiafava and Celli published in a number of articles the results of their studies of stained specimens of dried malarial blood.With the exception of small,spherical stained bodies in the red blood-corpuscles,which they thought might be micro-cocci,they interpreted the various other stained and usually pigmented bodies found in the red corpuscles of malarious patients as probably degenerative changes. As a matter of fact,the coccus-like dots were probably in part Ehrlich's degenerations,whereas their drawings show that the supposed degenerative forms were in real-ity the actual parasites,which,although not recognised as such,were in many of their phases actually depicted. It was in the year 1885,that Councilman and Abbott, in the organs from two cases of pernicious comatose fever found and described small pigmented hyaline bod-ies in and outside of red corpuscles,in the capillaries of the brain most abundantly.Marchiafava and Celli,in 1885,as the result of the examination of fresh malar-ial blood,came to a correct interpretation of these bodies,and described them fully and accurately.They

emphasised especially the amoeboid,unpigmented,transparent intracorpuscular bodies,to which they gave the inaccurate name of plasmodia,which has been widely adopted.They described clearly the intracorpuscular development of the parasite,the formation of pigment out of the colouring matter of the blood,the consequent changes in the blood-corpuscles,and they pointed out the probable reproductive nature of the segmenting bodies,which they described more fully and accurately than Laveran and Richard had done. We may here note that Marchiafava and Celli claim for themselves the discovery of the intracorpuscular amoeboid forms with and without pigment,and of the segmented forms,but,as is apparent from the review of Laveran's and Richard's preceding publications,this claim cannot be admitted. Marchiafava and Celli,however,described and interpreted these phases of the parasite far better than Laveran,and the credit of demonstrating the intracorpuscular development of the parasite therefore belongs to them. The publications of these two authors attracted wider attention than those of Laveran,and from the year 1885 up to the present time the literature upon the various questions connected with the parasitology of malaria has constituted a steadily flowing stream.As soon as the Italian observers had confirmed Laveran's discoveries,there came similar confirmation from Sternberg, Councilman,and Osler (1886-87),and somewhat later by James (1888) and Dock (1890),in America;and within a few years numerous reports from various parts of Europe, Asia,Africa,and other parts demonstrated the invariable association of Laveran's parasites with all cases of malarial fever.There are no observers of any prominence who,with sufficient opportunity and training for such examinations,have failed to recognise the parasites in cases of malaria;and our acceptance of the parasite as the specific cause of the disease has now no voice of dissent. Other observers,following the fundamental researches of Laveran,Richard,and Marchiafava and Celli (1880-85),have greatly extended our knowledge as to many details concerning the structure and life-history of the parasite and its relation to various types,phenomena,and lesions of malaria,although not a few important questions still remain unsettled.The most important of these later discoveries are due to the demonstration by Golgi (1885-86) of a definite relation between the cycle of development of the parasite and the different stages of malarial fever,and to the recognition by Golgi (1885-86) of the two varieties of the parasite belonging respectively to quartan and tertian fever,and by Marchiafava and Celli and Canalis (1889) of the variety or varieties belonging to the aestivo-autumnal fever.These observations have led to two schools of doctrine - the one (and that with the larger number of supporters),headed by Golgi and other Italian writers,upholding the plurality of malarial parasites,the other,headed by Laveran,holding the unity of a pleomorphic malarial parasite.The first to differentiate the three principal varieties of the malarial parasite in America was Dock (1890-92);since when a thorough study of the malarial fevers of Baltimore,with careful descriptions of these varieties,has been published by Thayer and Hewetson (op.cit.). Various observers (especially Celli and Guarnieri,

Grassi and Feletti,Romanowsky,Sacharoff,Mannaberg, Antolesei,Bastianelli and Bignami,and others) have made investigations concerning the intimate structure of the malarial parasites.

After the above historical note,we may further emphasise the factthat it is within the red blood-corpuscles of many kinds of animals that the malarial parasites of man are developed,and that they are of various species.They have been called haemosporidia by numerous writers;and it is in the red corpuscles of reptiles,amphibia,birds,and mammals that they are known to exist. To account for the natural history of these parasites is a matter of considerable difficulty and complication.Still,if we confine ourselves to the study of the best known species,namely,the parasites of warm-blooded animals,we may hold it to be a well-authenticated fact that they possess two life-cycles - the one being completed in the tissues of an insect, the other within the red cells of the warm-blooded animal.For instance,the parasites of Texas fever (bovine malaria) live in the red cells of cattle;from these they pass into a special kind of tick (Boophilus bovis,of Riley),then from the infected mother tick to its progeny,and this by pricking a healthy ox communicates to it the infection.So also with the parasite known as "proteosoma",which lives in the blood of birds; from these it passes into the middle intestines of a special kind of mosquito (Culex pipiens),where it goes through a whole life cycle,ending in the salivary glands of the mosquito,and when the latter stings healthy birds,infection of their blood in time occurs.In the case of human beings,the malarial parasites develop and multiply in the red blood-corpuscles of the affected person,where they go through an undetermined number of life cycles,and thence pass into the middle intestines of certain species of mosquito (Anopheles claviger,for instance),in which they go through the various phases of a new life cycle which ends in the poison-salivary glands;from these the parasite passes into man when the mosquito bites in order to obtain nourishment.From this it follows,then,that we have to study two cycles of life in connection with these parasites - one which is completed in man,and the other in some species of mosquito. Though these will in due course be considered in detail,the biological outline of the same may here receive brief mention.The cause of the malarial fever is the phase of life which is completed in man.In this phase the parasites,in their young stage,appear as many small amoeboid bodies endowed with more or less rapid movement and which exist within the red blood-corpuscles,by the substance of which they are nourished,converting the haemoglobin into black pigment;as they are nourished they increase in size,and lose a little of their motility,and (still within the globules) multiply by a process of fission.The daughter cells resulting from this fission become free in the plasma,and invade other red corpuscles in which latter the same cycle is commenced again. Intermittent fever and anaemia - the two salient phenomena of acute malarial infection - are intimately related to this life cycle.The first is manifested when the parasite is undergoing multiplication;the second is

produced principally through the destruction of a large number of red blood cells, which have gone in part to nourish the parasite. In all malarial parasites this cycle is completed in essentially the same manner. The structure is also fundamentally the same in all; it consists of a vesicular nucleus furnished with one or more small specks of chromatin, and by a ring of protoplasm, which during its development becomes pigmented by black granulations (melanin), representing the residua of the digestion of haemoglobin. The process of multiplication is identical in all: the chromatin increases in volume, and is divided into a number of tiny bodies; thus is formed a varying number of new nuclei, around which the segmenting protoplasm disposes itself. A residuum of segmentation, composed principally of black pigment, is, ~~finished~~ when the formation of the daughter bodies is completed, left remaining. Nevertheless, during the time that the life of these little beings is developing there are some differences to be noted in the various malarial parasites, which increase with the process of development. These differences, especially in the young forms, relate to the motility, which may be of several degrees; the minute characters of the pigment with which the protoplasm is loaded; the retrogressive changes undergone by the invaded corpuscles; the length of time necessary for the completion of the development of the parasite; the number of daughter bodies resulting from the division of an adult parasite, and certain points in connection with the occurrence of fission. It is a noteworthy fact that these differences constitute the morphological basis for the division of the parasites into various different species, which have constant characteristics, and do not become transformed into one another. It has from the earliest days been known that malarial fevers present different clinical characters, which permit of their being divided into various clinical groups or species. Recent researches have demonstrated that each of the malarial parasites is the cause of a special kind of malarial fever; so that, simply by examining the blood of a patient, we can authoritatively state the form of the disease from which he is at the time a sufferer. But, in addition to the life cycle in question which is completed in man, every kind of malarial parasite has another which only begins in man. Some parasitic bodies increase in size without dividing until they form bodies of characteristic shape and structure larger than a red blood-corpuscle. These bodies circulate in the blood for several days, without giving rise, when they are alone, to any morbid phenomena, such as fever or anaemia; then, remaining sterile, they degenerate and disappear. If the blood is subjected for a certain time to examination under the microscope, we shall find that some of these bodies throw out flagella which move with great rapidity, and, becoming liberated, move around the red corpuscles with vivacity, whereas others do not present this phenomenon. Special bodies, characteristic of one species of malarial parasite, - the aestivo-autumnal, called, from their appearance, crescent bodies, represent this phase of life. Numerous investigators have from time to time warmly debated the significance of these bodies. Indeed it is only comparatively recently, and

after a long series of erroneous conclusions,in some of which,however,there was a glimmering of truth,that we have now definitely ascertained that these bodies,which when they remain in man degenerate and disappear,are capable of further development when they pass into the intestines of certain species of mosquito.From them starts the second life cycle - a cycle which can be outlines as follows:When a mosquito of the right kind bites a sick person in whose blood are the crescent bodies or their homologues in other species of malarial parasites,some of these are taken in with the blood;then in the mid-intestine of the mosquito certain crescent forms give out the so-called flagella,which are motile filaments provided with chromatin;these filaments fecundate other crescent forms,which at this point become capable of penetrating,and travelling between the muscular fibres of,the mid-intestine.In view of facts,,then,it would seem that there is a differentiation of sex in the crescent bodies and their homologues in the other species of malarial parasites.These,becoming flagellated,represent,- to follow the nomenclature of the zoologists who have described similar phenomena in other sporozoa,- the microgametocytes,- cells producing the male elements,- while other non-flagellated bodies are the macrogametes,- female element.The fecundated macrogametes undergo their further development between the muscle fibres of the small intestines of the mosquito;then they are believed to take on a capsule,assume the aspect and characteristics of typical sporozoa,and increase progressively in size until they project into the cavity of the celoema;at the same time the nucleus divides into a great number of nuclei which become smaller and smaller,each one of which becomes the nucleus of a sporozoite.The latter is a small filament with very slender and usually curved extremities.It has at its centre a little nucleus at its centre,which has granules of chromatin and a few rods.A change now occurs in the capsules of the sporozoa;they break and become scattered throughout the body cavity.Many of them collect within the cells in some of the tubules of the salivary glands of the mosquito;and when the insect again stings a human being,they are inoculated together with the irritating secretion of the gland.This cycle from the small intestine to the salivary gland,is accomplished within a varying length of time - from eight to ten days or more,according to the temperature of the surrounding atmosphere.According to the species,moreover,of the malarial parasite,there are some slight differences. The parasites pass from man to the malarial mosquitos, and from these to man again with alternating generations.The cycle completed within the mosquito being characterised by forms of a higher development (segmentated forms),the malarial mosquito must be considered a definite lodging-place for the parasites;that in man must be held to be an intermediate abode,as it is characterised by a lower grade of development - amoeboid forms.The whole of the life of the malarial parasite is not yet,however,fully understood - at least whether or not this double life cycle is enough to insure the indefinite preservation of the parasites; that is to say,is it is possible for the latter to pass from the infected mosquito mother to the egg,and thence to the larva and the new generation of winged insects, as the parasites of bovine malaria (Texas fever) pass

from the infected tick to the young generation of ticks. Researches on this subject are still going on - the more recent of which are held by some to prove that the two life cycles - in man and mosquito - are sufficient to explain the known facts, and that there does occur hereditary infection in the insect in question.

We may here note that several names have been suggested for the parasite of malaria. Among these may be mentioned Oscillaria malariae (Laveran), Plasmodium malariae (Marchiafava and Celli), Haematomonas malariae (Osler), Haematophyllum malariae (Metchnikoff), Haemamoeba malariae (Grassi and Feletti), Haemococcidium malariae (L. Pfeiffer), Haematozoön or Haemocytozoön malariae (Osler, etc.), Haemosporidium malariae (Danilewsky); of which names that of Plasmodium malariae has gained wide currency. There is, however, no reason why it should be perpetuated, as it is on zoological grounds singularly inappropriate. There is much to be said in favour of the term Haemosporidium malarias, but it has not been generally adopted. Upon the whole, the name Haematozoön malariae, which expresses nothing as to the zoological classification of the parasite, and which has been adopted by many writers, may be provisionally accepted until more precise knowledge is reached concerning the zoological position of the specific cause of the disease. There is certainly the element of precision in favour of the term Haemocytozoön.

The unicellular organisms with the physiological characters of animals constitute the class known as the Protozoa, and to it the malarial parasite belongs. Bütschli divides the Protozoa into the orders - Sarcodinia, Mastigophora, Sporozoa, and Infusoria. Grassi and Feletti classify the malarial parasite among the Sarcodinia, subdivision Rhizopoda, and adopt the name Haemamoeba malariae. Antolisei considers that the parasite belongs to the Gymnomyxa, or, more precisely, the Proteomyxa of Ray Lankester. The great majority of observers classify the malarial parasite among the Sporozoa, which are divided by Balbiani into the groups Gregarinida, Sarcosporidia, Myxosporidia, and Microsporidia. Under the Gregarinidae are included the Coccidia, with which the malarial parasite is grouped by certain investigators. Under the Gregarinida Kruse makes a special family, which he designates as Haemogregarinidae, and to which he refers the malarial parasite and similar haemocytozoa in lower animals. Labbe gives the name of Gymnosporidia to the group the suggestion of which lies with Danilewsky, and termed by the latter Haemosporidia, in which the malarial parasite and similar haematozoa are arranged by him.

The various ways of studying and demonstrating the malarial parasite will be fully considered under the heading Diagnosis; but we may here note that the examination of thin layers of fresh blood with an oil-immersion lens is the most generally useful procedure. For the study of the finer details of structure the examination of stained specimens is necessary; and this method may be advantageously combined with the above-mentioned procedure.

GENERAL DESCRIPTION.

Life Cycle of the Malarial Parasite in Man.

It is now generally agreed that there are several species of malarial parasites, but there is great difference of opinion as to the number of species which

may be clearly distinguished,and as to the points of distinction between the same.The malarial parasite is a unicellular,protozoan organism which develops within the red blood-corpuscles,and therefore belongs to the group of Haemacytozoa.We shall see later that organisms closely resembling the malarial parasite have been found in the blood of birds.Our entire knowledge practically is derived from its study in human beings,though numerous attempts to cultivate the parasite artificially have been made.They have,however,been unsuccessful;and the organism has not been satisfactorily determined elsewhere.In all three varieties of parasite have been differentiated,which have characteristics so clearly recognisable that they must be considered as natural species.These are that of the quartan fever,that of the tertian fever,and that of the aestivo-autumnal (or summer-autumn) fever.Every one of these corresponds to a determined clinical species of malarial infection.The differences upon which these classifications are based are of various natures:in the first place,there are the morphological differences and those relating to the duration of the cycle of development;in the second place, we have the clinical differences in the disease which each of these species produces in man;in the third place,the epidemiological differences,or those relating to the geographical distribution of each species,and the various seasons in which there is a predominance of each of the species in question.Some observers hold that the so-called aestivo-autumnal parasites do not constitute a single species,but rather a group of distinct species - though all agree that the tertain and the quartan parasites are distinct.

It may be as well to consider the more important characteristics common to all varieties of the malarial parasite before dealing with the justification of the above-mentioned division,and the special characters of each of the varieties.According to the variety of the malarial parasite,the duration of the cycle of development varies from twenty-four to seventy-two hours;and it also comprises a vegetative and a reproductive stage. It is in the form of small,colourless,amoeboid,hyaline bodies, one to two mm.in diameter,that the vegetative phase begins;and it does so within the red blood-corpuscles. (We have already seen that Laveran believes that the forms of the parasite which have,since the publication of Marchiafava's and Celli's works,usually been regarded as within the red corpuscles,are attached or applied to the outer surface of the corpuscles.Mannaberg,in 1893,again raised this question by his statement that many of the amoeboid forms,particularly in their younger stages of development,are attached to the corpuscles,often in little niches or indentations on the surface.There is no doubt that the organism may be situated as described by Mannaberg.Marchiafava and Celli, who had previously noted this appearance,interpreted it as indicating the extrusion of the parasite from the red blood-corpuscle.It is,in fact,often very difficult to determine with precision whether the organism is on the surface of,or within the,corpuscle;but the evidence is that the the majority of younger forms are intracorpuscular.According to Marchiafava and Bagnami,1894,the

manner of penetration of the youngest forms into the corpuscle is as follows: "The youngest amoebae, the offspring of sporulation, by virtue of their viscidity of their protoplasm adhere to the surface of, and by their movements bury themselves in, the contour of the red corpuscles. In this position the parasite attacks the external strata of the corpuscle as a means of nourishment, and after altering these layers is able to penetrate within, and thus becomes entirely endoglobular.") These amoeboid forms increase in size, and, with the occasional exception of the aestivo-autumnal variety, they develop within them a variable number of dark pigment granules, situated, as a rule, near the margin of the parasite. The pigment, - which occurs in the form of irregular grains and of fine rods, which may be in active motion within the parasite, - increases in amount and in the coarseness of the granules as the organisms continue to develop. The parasite - having attained a certain stage of development, which differs as regards the size of the organism in different varieties - gradually ceases its amoeboid movements, assumes a spherical or oval shape, and becomes somewhat sharper in contour. In this condition it may continue for a while to grow. When it has reached its full size - when it may now be called the full-grown or adult form - it may completely fill the red blood-corpuscle or may occupy only a small part of it, these differences depending mainly upon the variety of parasite. The enveloping red blood-corpuscle may, coincidently with these stages of development, undergo various changes, which are of significance in distinguishing the varieties of parasite from each other. The corpuscle may become swollen and pale, or shrunken, or brassy-green in colour, or otherwise deformed, or it may appear unaltered in its appearance. In this cycle of development the subsequent changes belong to the reproductive phase, which is shorter in duration than the vegetative. The first eveidence of this reproductive phase is the collection of the pigment into a mass of granules or a solid block situated usually at or near the centre, but sometimes near the periphery, of the organism. In accordance with the suggestion of Thayer and Hewetson, the term "presegmenting forms" - the "corpi con blocchetto" of the Italian physicians - might be used as a designation. The process of segmentation begins coincidently with or following this gathering of the pigment into a clump, sometimes without a definite collection of the pigment. In its most typical form segmentation is ushered in with the appearance of delicate lines radiating from the periphery towards the centre. Eventually the substance of the spherical organism is divided into a number of round or oval bodies called spores. The enveloping red corpuscle, which now may be reduced to a narrow pale rim, bursts, and the spores are set free; or the corpuscle may have disappeared before the process of segmentation is completed. The pigment remains behind, and is quickly engulfed by the phagocytes. Sometimes in the aestivo-autumnal variety segmentation occurs in organisms entirely devoid of pigment. "Sporulating forms" is a term used to indicate these segmenting bodies. The next thing that happens is that the free spores speedily invade fresh red blood-corpuscles, where, as in the small, colourless, amoeboid, hyaline bodies already mentioned, they begin again the cycle of development. Plehn claims to have

observed that the spores are actively motile and flagellated,but this statemtn is opposed to the observations of others.The direct transformation of the motionless round spores into the small,hyaline,amoeboid bodies has been very rarely observed;but there is no reason to suppose that between these two forms there exists any intervening stage.Therefore,we can distinguish the following forms of the parasite in the complete sporulating cycle of development just described: Unpigmented, amoeboid,hyaline bodies;pigmented,amoeboid,hyaline bodies;full-grown or adult bodies;presegmenting bodies; segmenting or sporulating bodies;and spores. We have already seen that,in the aestivo-autumnal variety,this cycle may be completed without the appearance of pigment. These bodies are to be thought of,not as separate and distinct forms,but simply as successive stages of development with all transitions from the youngest to the most advanced.Especially can no sharp distinction be drawn between the unpigmented,amoeboid,hyaline bodies, the pigmented,amoeboid,hyaline bodies,the full-grown or adult bodies,and the presegmenting bodies.The recognition, as a distinct form,of the body designated as presegmenting is of less practical importanve for the quartan and tertain varieties than for the aestivo-autumnal.To the unpigmented,amoeboid forms the name "plasmodium" was originally applied by Marchiafava and Celli.It is frequently employed to designate both the pigmented and the unpigmented amoeboid bodies (which may be called,in general,hyaline forms or amoebae),as well as the parasite in all of its forms.We shall presently see that it is only the quartan variety that is found in all its forms with equal frequency in the peripheral circulation and in the blood of the internal organs;whereas segmenting tertian parasites are more abundant in the spleen and bone marrow than in the peripheral vessels,and the aestivo-autumnal parasite develops mainly in the internal organs,in the peripheral circulation its segmenting forms being extremely rare.One may also find free in the plasma each of the forms of the parasite which have been described within the red blood-corpuscles.They probably escape by rupture of the enveloping corpuscle,a process which one may often witness when examining the fresh blood microscopically.Extracorpusclular mature forms may possibly segment in the usual way;but the completion of the cycle of development free in the plasma as regards forms in the earlier stages has never yet been satisfactorily determined.Golgi made a very important discovery - viz.,that all of one generation of the parasite form a group,the members of which develop approximately at the same time,and that a definite relation exists between the phases of development of the parasite and the stages of malarial fever. The onset of a paroxysm corresponds to the ripening of one generation of the parasite.A few hours or shortly before the paroxysm segmenting forms appear,and enable the observer to predict the approaching paroxysm.The spores which are set free by the act of sporulation invade the red blood-corpuscles and start a fresh generation,which pursues during the paroxysm and the subsequent apyrexia so regular a development that in typical cases the experienced observer can tell approximately - by examination of the blood - the stage of the disease:that is to say,the

time which has elapsed since the last paroxysm and the time that one may expect the next one. Nevertheless, it is not always the case that the parasite develops with the regularity expressed by Golgi's law; and especially in the aestivo-autumnal fevers irregularities are very common. The simultaneous occurrence of two or more generations, in different stages of development may render difficult the interpretation of the phases observed, although even here the observer will be able to draw correct conclusions in tertian and quartan fevers if he takes sufficient care in procedure. It has not yet been completely proved that there occurs any other cycle of development of the malarial parasite in human beings than that which has been described above, although the possibility of such is by no means negatived. Canalis, in 1889, stated that he believes that he has found evidence that a second, slower cycle of development of the aestivo-autumnal parasite occurs, which is represented in certain of its phases by bodies of the crescentic group. to be be described subsequently; and this doctrine, - which is opppsed by many observers, and does not at present rest upon sufficient evidence, - has been accepted by Antolisei and Angelini, Grassi and Feletti, and Sacharoff. On the basis of clinical evidence, it seems necessary to suppose that the malarial parasite may remain for months in a latent condition in the human body, and then begin to develop again, causing a relapse of the fever. As such relapses may occur in forms of malaria in which crescentic bodies do not appear, there must be in these cases some resistant organism other than bodies belonging to the group of crescents. We know practically nothing as to the nature of these resistant bodies. The hypothesis is advanced by Bignami that they may be spores which are enclosed within leucocytes and other cells, and which have become surrounded by a resistant membrane and have lost their usual affinity for the ordinary stains. It is worthy of note that, besides the forms already described as representing phases of the regular sporulating cycle of development of the malarial parasite, there occur other forms which cannot be referred to any cycle of development. These other forms are three in number - viz., crescentic bodies and fusiform, oval, and round bodies belonging to the same group; flagellate bodies and free flagella; and degenerative forms. From their size and appearance (which is remarkable) the crescentic and flagellate bodies are the most striking forms of the parasite, and from the beginning have attracted considerable attention. We do not exactly know what is their significance, though sundry theories have been advanced thereon. Regarding the first mentioned, the crescents develop only from the aestivo-autumnal parasites, - never from the tertian and quartan parasites, - and will be duly considered in connection with the same. On the other hand, the second-mentioned, the flagellate bodies, may form from each variety of the parasite - tertian, quartan, or aestivo-autumnal. The weight of the evidence is that they do not exist in the circulating blood, but develop after the blood has been withdrawn from the body, usually within ten or twenty minutes and sometimes earlier. Some observers have found them frequently, others very rarely. They are frequently found if the blood is examined at the right stage of the disease, and time is allowed for

their development.Councilman showed that they are more commonly found in the blood aspirated by a hypodermic needle from the spleen than in the peripheral blood. They develop in tertian and quartan fevers from the mature,full-grown extracorpuscular forms - in tertian especially from the swollen forms larger than the red blood-corpuscles.They are therefore found most frequently a short while before and during the paroxysm. In infections with the aestivo-autumnal parasite the flagellate bodies develop from round bodies belonging to the group of crescents,and do not occur in definite relation to the stage of the febrile attack.Flagella are seldom developed by the intracorpuscular bodies.There is always,or nearly always,pigmentation to be seen in connection with the spherical bodies which become transformed into the flagellate bodies.Marchiava and Celli state that they once saw an unpigmented flagellate body.These bodies may be somewhat smaller or larger than the red blood-corpuscles,the size varying to some extent with the different varieties of the parasite,as we shall presently see.The process of development of the flagella may be studied under the microscope.The pigment granules, which at first (aestivo-autumnal variety) may have been in repose,usually begin to dance about within the organism,often in a lively way.In the aestivo-autumnal variety they usually gather in the central part,but in the others they may be near the periphery or irregularly distributed.The spherical body may acquire an oscillatory or jerking movement.Projections may be formed and retracted at the periphery,and the whole edge may acquire a vigorous undulating movement.These changes are attributed to the movementsof the flagella within the body or in the peripheral layers,and have been graphically been compared by Richard to the struggles of an animal to get free.Suddenly,the flagella shoot out from the periphery,and with their active lashing movements produce a violent commotion among the red blood-corpuscles and the other small particles which may happen at the time to be in their vicinity.On examining the flagella closely,we will observe that they are pale and thin,presenting often at their extremities and along their course small olive-shaped swellings which may change their position.Here and there a pigment granule is occasionally seen in flagellation.The flagella vary in size,number,and position.Their length may be three or four times the diameter of a red blood-corpuscle,or not more than half that size.One to six may be attached to the spherical body.They may project from one side or from any part of the circumference of the body. Their movements may be somewhat rhythmicallthey may become slow or even cease,and start up again.Among the red blood-corpuscles one may observe free movement of the flagella which have become detached.On account of their pallor,such free flagella would usually be overlooked were it not for the commotion which they produce among the red blood-corpuscles.For half an hour,or sometimes longer,is usually the duration of movement of the flagella on the slide.The most striking forms of the malarial parasite are these flagellate bodies;and the fact of their being a living parasite is at once apparent on examination.It is not surprising that they attracted in an especial manner the attention of Laveran,who,as already mentioned,regarded the flagella as the most characteristic and perfect form of development of the

parasite. Subsequent studies have not, however, tended to confirm the conception of Laveran as to their significance. As has already been made clear, the flagellated bodies do not belong to the regular sporulating cycle of development of the malarial parasite in the blood of man. There are various theories as to their significance, of which the following are the most prominent: (a) They are forms of degeneration, or appearances belonging to the death-agony of the parasite. In support of this view it is urged that the flagellate bodies do not belong to any known cycle of development; that they are developed only outside of the human body; that they are developed from mature forms which are known frequently to undergo undoubted degeneration, such as hydropic swelling, vacuolation, and fragmentation, and which may already showing beginning evidences of degeneration; that nuclear substance is absent from the flagella; and that known to zoologists, and interpreted as degenerative, are similar appearances of extrusion of motile filaments in other unicellular organisms. (b) From a study of their structure on stained specimens, Sacharoff believes that the process is degenerative, and that the flagella are extruded chromatin filaments derived from perverted karyokinetic nuclear division. (c) That the flagellate bodies "represent resting states of the organism, capable of existing independently, perhaps even of reproducing themselves, but also able, under favourable circumstances, of reproducing the typical growth of the parasite," is suggested by Dock. (d) No less an authority than Mannaberg holds that the flagellate bodies may represent a state belonging to the saprophytic existence upon which the mature forms of the parasite enter soon after the blood is withdrawn from the body. On account of the suitable conditions of environment, they are unable to continue their existence in the blood outside of the body and soon perish. A similar view is advanced by Manson, who suggests that the flagellate bodies represent the first stage, and the detached flagella, in search of their appropriate host, represent the second stage of life of the parasite outside the body. Manson (The Goulstonian Lectures on the Life History of the Malarial Germ Outside the Human Body. Brit. Med. Jour., 1896, Mar. 14, 21, 28) lays much emphasis upon the supposed analogies between the malarial germs and the filaria sanguinis. The correctness or otherwise of his theory will be determined only by future investigations. The same author conjectures that the mosquito is the extracorporeal host of the malarial parasite, and the observations of Ross, showing the development of flagellate forms in the stomach of mosquitos fed on malarial blood, are reported by him. For and against each of these theories there are arguments. In spite of one's natural reluctance to consider such striking forms as the flagellate bodies as phases of degeneration, the existing evidence seems upon the whole in favour of this hypothesis more than in favour of any other which has been advanced. Still, if Sacharoff's observations as to the presence of nuclear material in the flagella be correct, the objection of Grassi and Feletti, that the flagella are incapable of reproductive development because the nucleus of the parasite does

not divide and enter them,would be overthrown and the hypothesis of Mannaberg and Manson would become more probable.Though a term commonly employed,it is evident from the description of these bodies that the use of the word flagella to designate the motile filaments is of doubtful propriety. Besides the flagellate ones, there are various bodies,often seen in the examination of malarial blood,which are undoubtedly degenerative forms of the parasite,and others which are probably degenerative,although opinions concerning the latter are divided.The more common signs of degeneration of the parasite are vacuolation,pseudo-gemmation,fragmentation,deformities of shape,particularly swelling,granular condition of the protoplasm,certain alterations in the arrangement and appearance of the pigment,disappearance of nuclear material,defects and irregularities in staining,and changes in refraction of the organism. These various degenerative changes produce forms too numerous to describe in detail.They have often been misinterpreted,and described as special forms of the parasite,some of them as special modes of reproduction, particularly certain vacuolated and budding forms. In any form of the parasite degenerations may occur,but they are particularly common in the extracorpuscular forms.Mannaberg describes the disintegration of young intracorpuscular forms,with disappearance of their nuclei.Fragmentation of forms extruded from the blood-corpuscles can sometimes be watched before examining fresh blood under the microscope.As a rule,only a certain number of mature forms actually enter into reproductive segmentation,and many of the spores or segments perish. If all segmented and the offspring survived,the number of the parasites after a few paroxysms would become enormous.As a matter of fact,degenerations of full-grown parasites are often observed.An interesting form of such degeneration,found most frequently in the mature forms of the tertian variety,is the appearance of swollen,pigmented,so-called hydropic bodies,often much larger than red blood-corpuscles,and sometimes containing vacuoles.Round bodies simulating spores are sometimes seen in these vacuoles,but on properly stained specimens they are devoid of the nuclear material of genuine spores.Pseudo-gemmation,or appearance of sarcodic buds on the surface of the organisms,is doubtless a form of degeneration.Such buds may become separated,in the form of hyaline balls,from the parent organism.These evidences of degeneration may appear also in crescents and bodies belonging to this group,and in flagellated bodies.From the latter small hyaline balls,with a flagellum attached,may break off and move around actively. Such bodies look like flagellated spores,but they are not such.Multiplication of the malarial parasite,by budding or simple cell-division,has never yet been satisfactorily established.Although it cannot be denied that other forms of reproduction may exist,the only form of multiplication which has been demonstrated is that of sporulation,also called segmentation,already described.For a time it was the belief of Celli and Guarnieri that spherical bodies of the crescentic phase may multiply by the formation of buds (gemmation);but they subsequent abandoned this view,and adopted the now

generally accepted opinion that these budding forms are degenerative.The structure of genuine spores is absent from these so-called buds. Quinine is capable of producing various interesting changes in the parasite, of a degenerative character,which will be described in due course. It is evident that,as the malarial parasite passes its vegetative life mostly within the red blood-corpuscles,it finds its food in this situation. This food may be appropriated both by intussusception and by diffusion.Evidence of the former is found in the occasional presence of fragments of corpuscular substance within the body of the amoeboid forms.That diffusion is the more important mode of nutrition is doubtless true. Many have sought to discover whether the malarial germ may develop in other cells of the body than the red blood-corpuscles.Nearly all forms of the parasite have been found enclosed in cells,chiefly leucocytes, splenic or medullary cells,and endothelial cells.As such included parasites often present evidences of degeneration,these appearances have been generally interpreted as referable to phagocytic destruction of the parasites, and such they unquestionably usually are.Golgi and Monti have,however,published observations intended to show that the aestivo-autumnal parasite may develop within endothelial and other cells.In the condition in which it exists in the human body,the malarial parasite is very susceptible to injurious agencies.It is quickly killed by the addition of distilled water and of dilute acids and alkalies.Under ordinary conditions it does not long survive in blood withdrawn from the body.Un der certain special circumstances it has been kept apparently alive for two to four days,possibly for a week. Sacharoff observed amoeboid movements in the aestivo-autumnal bodies which had been for a week in the intestinal canal of leeches kept on ice;and he obtained a positive result by inoculating himself with malarial blood obtained and preserved in this way for four days in leeches.The tertian and quartan parasites were found to be less resistant than the aestivo-autumnal.The parasite does not continue to develop and multiply after death in the human body.Ripe bodies may segement in blood outside of the body,but no further development or multiplication of the parasites has been positively observed in the various attempts made to preserve or cultivate them. As to the nature of the parasite in its natural condition in the outer world no inferences can, of course,be drawn from these observations.Grassi and Calandruccio have thought that certain species of amoebae which they have observed in malarial districts might be the extraparasitic form.The failure of artificial cultivations and certain analogies drawn from the zoological characters of the parasite have led to the prevalent theory that the malarial parasite passes at least a part of its existence as a parasite in animal or vegetable organisms.The affirmation as to the mosquito being a host for the malarial parasite has already been mentioned.Though malaria can be transmitted by inoculating into healthy individuals,either subcutaneously or intravenously,blood from a malarial patient,there is no evidence that the malarial parasite is eliminated from the human body in a condition capable of infecting another individual or the locality.That the germ is

capable of entering u on some resistant phase of development seems highly probable in view of the evidence that malarial fever can be contracted from the air.

The Malarial Parasites.

Concerning the nature of the malarial parasite much controversy has raged in the past. We have already seen that there are two schools of opinion as to this: the one led by Laveran holding that the malarial parasite is a single species with pleomorphic characters, the other believing that there are three or more species, or at least varieties, of the malarial parasites. Investigations in malarious regions have supported the latter theory, which originated with the Italians. In 1885 and 1886, Golgi first differentiated the parasite of quartan fever from that of tertian fever; and Marchiafava and Celli and Canalis, in 1889 and 1890, differentiated the variety of the parasite characteristic of aestivo-autumnal fever. The credit of having first discovered the aestivo-autumnal parasite has been warmly contested by Canalis on the one hand, and Marchiafava on the other. The differentiation of this parasite was not made all at once, and with the same precison in all details, as in the case of Golgi's sharp separation of the quartan and tertian parasites. From the beginning of his researches, Golgi suggested (1885-86) that the crescentic bodies belong to a special cycle of existence different from that of the tertian and quartan organisms, and noted their occurrence in irregular malarial fevers. Councilman, in 1887, emphasised the association of crescents with remittent fevers and malarial cachexia. In February, 1889, Golgi definitely expressed the opinion that, in addition to the malarial fevers caused by the quartan and the tertian parasites, we must recognise another type of fever associated with unpigmented amoeboid forms and crescents. There appeared, on September 13, 1889, a preliminary communication of Marchiafava and Celli, which must be regarded as furnishing the first clear and sharp description of the essential differential characters of the aestivo-autumnal parasite, with especial emphasis on the occurrence of unpigmented organisms. On October 10, 1889, appeared the preliminary communication of Canalis, in which likewise the essential characters of this parasite was described; and a greater emphasis was laid upon its relation to the crescents than had been done by the two authors just mentioned. There is much difference as to the number of the aestivo-autumnal parasites. All adherents of the doctrine of plurality agree that there at least three varieties of malarial parasites - viz., the quartan, the tertian, and the aestivo-autumnal - distinguished from each other by morpholigical and biological characters to be subsequently described. Thtough there reamin many unsolved probelms for the future to clear up, the discovery by Golgi of the definite cycle of development of the malarial parasite and the recognition of several distinct varieties have done much to bring order out of the earlier chaotic condition when a multitude of parasitic bodies were described without knowledge of their significance or mutual relations. That all the so-called varieties of the parasite may be explained simply as phases of

a single pleomorphic organism - influenced by various conditions od environment,such as locality,season, individual predisposition,and various unknown circumstances - is an hypothesis urged by Laveran in oposition to the doctrine of plurality.He contands that the characters upon which a devision into separate varieties is based are insufficient for such a purpose and inconstant;that one so-called variety under certain conditions may be tranformed into another;and that there is no definite,necessary relation between the types of fever,such as quartan,tertian,quotidian,irregular, continued,and the form of parasite present. He argues that the doctrine of plurality is not supported by the experimental production of malaria by inoculation; and he emphasises the view that malaria,with all its diverse manifestations,is,nevertheless,clinically and anatomically one disease,and has always been so regarded.Hethinks,also,that the variations of the malarial parasite can be explained in large part by the varying rapidity of development.Now,when we come to consider the force of these objeftions of Laveran's,it must be admitted that ,as we are unable to cultivate the malarial parasite artificially,and are ignorant of its life-history and the conditions of its existence outisde of the human body for the most part,the possibility must be admitted that under certain conditions,at present not fully understood,one variety may be transformed into another.But,on the other hand,the existing evidence (and it is already considerable) goes to show that under the conditions which we can at present control and study,each of the three principal varieties of the parasite preserves its identity and is not transformed into another variety,- e.g.,the quartan into the tertian,or either of them into the aestivo-autumnal.There are various arguments in favour of the doctrine of plurality,of which the following are,in brief,the principal: (1)Each well-eastablished variety of parasite presents morphological and biological characters which are sufficient to identify it.(2)They each correspond to definite types of fever.Genuine quartan fver can be produced only by the quartan parasite. As will be explained in the clinical part of this essay, other types of fever may be caused by more than one variety of parasite,and much complexity may result from multiple and mixed infections and various irregularities;but the recognition of certain fundamental types of fever,characteristic of each variety of the parasite,is not presented by this.(3)Grassi and Feletti,and Calandruccio have carefully studied,for weeks or months, cases of pure infection with one variety of parasite without any indication of the transformation of one variety into another.One cannot interpret in favour of the metamorphosis of one variety into another the appearance of a second variety of parasite in localities where there is opportunity for renewed infection. (4)One encounters only one or two varieties of the parasite in certain localities.In a few places only the quartan,or more frequently only the tertian,parasite is observed;in most places where malaria is mild and infrequent,only tertian - and occasionally quartan - parasites,with entire absence of aestivo-autumnal parasites,are found.(5)The experimental production of

malaria furnishes strong arguments in favour of the constancy of the varieties of the malarial parasite. In 1882 and 1883, Garhardt was the first to produce malaria experimentally by the subcutaneous injection of blood obtained from malarial patients. At this time the malarial organism was not generally recognised. Since these first experiments similar ones have been repeated, usually in the manner of intravenous injections of malarial blood, with positive result in a large number of cases. The experiments before 1889 were made without determination of the exact variety of parasite injected and found in the experimental case. In 1889, Gualdi and Antolisei, without full knowledge of the critical nature of the experiment, injected two patients intravenously with 3 c.c. of blood from a patient suffering from quartan fever, and possessing quartan parasites. In each of the inoculated individuals irregular fever with aestivo-autumnal parasites developed. These two cases are constantly adduced as a main support of the doctrine of mutability of the varieties of the parasite, but unjustly so, for it was subsequently determined that the patient from whom the blood was obtained had previously suffered from irregular fever, and he subsequently developed characteristic aestivo-autumnal organisms; so that the experimenters themselves have expressed the opinion that at the time of the inoculation the patient furnishing the blood had combined quartan and aestivo-autumnal organisms, the latter being overlooked. In view of the uniform results yielded by the numerous subsequent experiments in support of the doctrine of immutability of the varieties of the parasite, there can be little doubt that this later opinion of Gualdi and Antolisei is correct. It has been found regularly since these experiments that if blood containing only the quartan or the aestivo-autumnal parasite be injected intravenously into a person unaffected with malaria, the variety of the parasite injected, and only that variety, appears in the blood of of the experimental case. When the two varieties of parasite are injected, or when the malarial blood is injected into a patient already affected with a malarial organism other than that injected, then it usually happens that one variety supplants the other, most frequently the one injected supplanting that already existing in the individual subjected to inoculation. The numerous inoculation experiments, showing the identity of the parasite in the experimental case with that in the blood used for injection, furnish the strongest arguments in favour of the malarial parasites being more than one only.

Classification of Malarial Parasites.

The parasites of malaria have been classified in various ways, some observers placing them amongst the Rhizopoda, others regarding them as Sporozoa. For various reasons, Golgi classed them with the rhizopoda in his earlier researches; but chiefly because he thought it certain that these parasites multiplied in the free state, whereas the sporozoa never do. They appear as typical sporozoa in the mosquito. Labbé, Metchnikoff, and Danilewsky are amongst those who maintain that these parasites belong to the class of sporozoa; and the classification has apparently found a firm support from more recent researches into the life cycle of the parasite outside of man. The protozoa lead a parasitic existence and multiply by sporulation. The Sporozoa are

such;and this class has been divided into various orders and sub-classes,- e.g.,Gregarinidea,Coccidiidia,Myxosporidia,Sarcocystidia,Microsporidia,to which Mingazzini has proposed the addition of the sub-class Haemosporidia.All the parasites that are found in mammals,reptiles, frogs,and birds are included in the latter. Labbé, however,divides the parasites of the blood into two orders which he classes under the sporozoa - the Gymnosporidia (including the parasites of man,which he calls Haemamoeba Laverani),and the Haemosporidia.Plasmodium (parasites of man),Haemogregarina (Drepanidum -parasites of the frog),and Haemoproteus (parasites of birds) are the three different genera under which Cell,Kruse,and Sabfelice group all species. On the other hand, two genera are recognised by Grassi and Feletti to comprise the malarial parasites and the forms related to them: First,the genus Haemamoeba,which includes the following species: Haemamoeba malariae (quartan parasites),Haemamoeba vivax (tertian parasites),Haemamoeba praecox(pernicious parasites),and Haemamoeba immaculata (pernicious). To these may be added another group of species,which are the parasites of birds:the Haemamoeba relicta(in the sparrow,lark,etc.),the subimmaculata (in the Hawk),and the subpraecox (in the lark,owl,etc.).Second,the genus Laverania,to which belongs a species that lives in man,Laverania malariae (crescent parasites);and other parasitic species im other animals - e.g.,Laberania ranarum (in the edible frog),and the Laverania Danilewsky (in many pigeons,sparrows,and birds of prey). As already mentioned,Laveran is among the few to hold that the parasite of man is a form of species which is polymorphous - one species with variable development. The various febrile types,he thinks,are not due to differences in the parasite,but to a,as yet unknown,disposition on the part of the affected organism: in fact,he states that there are many cases of fever in which there is no constant relation between the febrile type and the parasitic form. This last statement of Laveran is contradicted by all modern researches; and the view held in general by the Italian observers,who,following Golgi,distinguished various species of malarial parasites,in intimate relation with the variety of the febrile seizure,may be adduced in opposition to that distinguished investigator's opinion. According to whether or not there is a formation of syzygies, Mannaberg divides the parasites into two groups:First, parasites with sporulation without syzygies - i. e., parasites without crescentic forms:the same to include the tertian and the quartan forms of the disease. Second,parasites with sporulation and with the formation of syzygies (crescents);the same to include the malignant tertian parasite,the pigmented quotidian parasite, and the non-pigmented quotidian.It is worthy of note that,as regards the fundamental basis of this classification,it is not possible to contrast the aestivo-autumnal parasites(Mannaberg's second group)with those of the tertian and quartan:by reason of the presence of absence of crescent bodies.Indeed,it has now been demonstrated that in the tertian,for instance,there are parasitic forms - large mononucleated pigmented bodies - which have the same biological significance,and the same ulterior development,as the crescent forms. As to the

subdivision of the second group,it is held that there is not as yet sufficient proof to allow of the admission that the parasites which complete their entire cycle without becoming pigmented represent a species by themselves,although the probabilities point that way. In spite of the distinction of the aestivo-autumnal parasites into quartan parasites and parasites of the malignant tertian,these two forms are not looked upon as distinct species,but as closely related varieties of the aestivoautumnal parasites.By classifying the malarial parasite into the three species of aestivo-autumanl, tertian,and quartan parasites we take into consideration only the best proved facts,leaving out all disputed points;so that,if we examine the classifications proposed by the various authors,we find that,in spite of divergences,they all agree in considering the three species as distinct.It is likely that the first includes several closely related varieties.If we leave out of account these considerations of secondary importance, we find that there are three arguments upon which the division of the malarial parasites into the abovementioned species rests - viz.:First,in all essential morphological and biological characteristics the three species exhibit perfect constancy,- which same have been noted everywhere where malarial fever abounds,- so that they can easily be recognised on examination under the microscope. Second,a determined clinical species holds an indisputable and close relation to them. Third,they are capable of being inoculated from man to man;and, without ever being transformed into another,each reproduces its own form. A fact of scientific importance and of great practical value is constituted by the constancy of the morphological characteristics,because it permits us to make with positiveness the differential diagnosis between the three species of parasites described:from a prognostic point of view,also,a fact of no inconsiderable importance.Both morphological and biological are the differences between the quartan and the tertian parasites,so that the two can easily be distinguished by a capable investigator.Indeed,the differences are four in number - viz.: First,differences in the developmental cycle - the ordinary tertian parasite completing its whole life cycle in two days,one day more than that being necessary for the quartan to do so. Second,Differences in the character of the amoeboid movements,the quartan having less active movements than the endoglobular amoeboid forms. Third,differences in the behaviour of the parasite towards the substance of the red blood-corpuscles,the tertian parasite discolouring the red cell much more rapidly than the quartan and more decidedly.Furthermore,the cells invaded by the tertian parasite become swollen and perhaps tend to become smaller,whereas those invaded by the quartan either preserve their normal size,or tend to become smaller,than the red blood-corpuscles.Fourth,differences in the morphological characters.The pigment granulations of the tertian are extremely fine;those of the quartan haemamoeba are larger.The quartan parasites have better defined and clearer outlines than the tertian.There are some diff rences to be found in the sporulating forms.These consist in the number of bodies resulting from fission,- gymnospores,- which average fifteen to twenty in the tertian parasites,six to

twelve in the quartan;and in the size of the individual bodies,which is larger in the quartan.Moreover,within each spore resulting from the segmentation of the quartan amoeba we see a central shining sphere,which represents the so-called nucleolus or nucleoliform body; but in the tertian gymnospore this is not of constant occurrence.The differential diagnosis between the parasites of the ordinary tertian and that of the aestivo-autumnal tertian is always easy;for the differences - which same relate to the size of the parasite and the appearance of the parasitic forms - are very marked.Now,regarding the size of the parasite,the parasites of aestival tertian, at the same stage of development,are always than those of the ordinary tertian appear to be.So far as the appearance of the parasitic forms is concerned,the aestival parasites,in their first phase of life,long preserve the property of taking on the characteristic annular form in fresh preparations;similar rings are seen in the ordinary tertian but rarely,and they are never seen at an advanced stage of development.Moreover,the annular and discoid forms of the aestivo-autumnal parasite have more distinct outlines,and stand out more conspicuously against the backgroud of the red blood-corpuscle than the corresponding forms of the ordinary tertian do. It should alaso be noted that there are four other differences worthy of consideration;and these are the characteristics of the pigment,the alterations produced in the invaded red blood-corpuscles,fission forms,and the forms which begin in man the life cycle which is continued in the mosquito.In the ordinary tertian the pigment is abundant and nearly always motile;it is in very fine granules,rarely motile,and arranged for the most part upon the extreme margin of the amoeboid body in the parasites of the aestival tertian.When the red blood-corpuscles are invaded,these swell with great rapidity in the ordinary tertian;while they tend to become smaller and to shrivel - the colour of the haemoglobin becoming deeper than under ordinary circumstances - in the aestival tertian.Fission is accomplished by a similar process in the two forms of tertian;but the completely sporulated forms ate usually much larger in the ordinary tertian,and the individual gymnospores are larger than the parasites of the aestival.The forms which begin in man the life cycle which is continued in the mosquito are represented in the ordinary tertian by the large, round,pigmented bodies above-mentioned;whereas in the aestivo-autumnal parasites - aestival tertian - they are represented by the characteristic crescents.Furthermore, the flagellated bodies of simple tertian usually possess a larger number of flagella than those of crescent origin exhibit;and,finally,it may be noted that there are other differences relating to some biological properties -e.g.,the pathogenic action on man,and the distribution of the parasitic forms in the circulation.We may safely affirm that at the present time no doubt can be cast upon the possibility of distinguishing these three species by microscopical examination of them alone;for the differences between the tertian,the aestivo-autumnal,and the quartan parasites have,since the studies pursued in Italy,been recognised by nearly all investigators who have taken up the subject.The sstablishment of the opinion that we are dealing with distinct species, not intertransformable,has been greatly contributed to

by the results of the injection of malarial blood in man.These experiments show that when blood containing one kind of parasite only - as,for instance,the quartan or the tertian - is injected under the skin or into the veins of a healthy person,parasites identical with those injected will be developed,and a fever,similar to that in the person from whom the blood was taken,will be caused.We find that,among all the inoculation experiments which have been made,only two that appear at first sight to be opposed to the theory of distinct species. These relate to two patients of Gualdi and Antolisei, in whom they injected blood with quartan parasites,with the result that one of the patients developed a fever with aestivo-autumnal,and the other with tertian parasites.Still,one may call in question the statement that only two experiments furnish valid arguments in support of the belief that the parasitic forms of quartan can be transformed into aestival or tertian forms.Antolisei gives a critical review of these two cases,in which he states that the patients from whom the blood for the experiment was taken had in the last few months suffered from fevers of various types - quartan,tertian,quotidian, and irregular.Therefore,it is evident that in the blood of these patients there coexisted the germs of three species of malaria,but in varying quantity;so that the existence of a mixed infection had escaped the notice of the observers,and they supposed that they were using the blood of a person with pure quartan for the inoculation.Indeed,the same observers always obtained the reproduction of the same form in the person inoculated,in subsequent experiments in which they used the blood of patients with a recent and pure infection.The majority of recent investigators have recognised the intimate relation between the three parasitic species and the clinical forms of malaria.Each species of malarial parasite differs from the others in respect to the pathogenic action upon man,as a study of the various species of malaria will show.Much is made of the fact,by the supporters of the doctrine of polymorphism,that it is not infrequent to see the same patient affected by different types of fever with different species of parasite.But this merely proves that the parasites and the various febrile types can succeed each other alternately in the same patient,and does not in the least demonstrate that they are transformed into one another.Facts such as these only prove that,in mixed infections given by two species of malarial parasite,the two infections tend rather to succeed each other than to coexist.This is shown by several interesting experiments of Di Mattei,who,having inoculated quartan parasites into a patient who had crescent forms in his blood,saw the crescent infection disappear and the quartan develop;and,on the other hand, he saw an aestival infection develop and the quartan disappear upon inoculating,with semilunar blood,a quartan patient.We must also remember,with a view to explaining the succession of febrile types and of the various parasites in the same person,that mixed infections due to two kinds of parasite may coexist,while only one of them exhibits characteristic clinical manifestations. For instance,we frequently see patients with aestival tertian who have tertian parasites in the blood in addition to the aestivo-autumnal parasites.In spite of

this,the grave clinical forms of aestival tertian keeps the first place,and interferes with a recognition of the mixed infection,unless the blood be examined.But,as a rule,the tertian parasites very soon disappear from the circulating blood,and the aestival affection is to all appearances pure;this does not prevent the occurrence of an ordinary tertian in its typical form and with characteristic parasites in the relapses after several months' interval.This fact has been adduced in support of the idea that the aestival parasites could be transformed into the tertian,with a corresponding transformation of the febrile type.But the fact that the infection was a mixed one from the beginning,and that during its course the parasites alternated - each one causing its own special type of fever - will be demonstrated on accurate observation.Therefore,the apparent transformation of the febrile type may be due to the fact that in a mixed infection one of the parasitic species may remain latent for a long while,and then,from some cause or other,may reappear with its characteristic febrile type.The view that all the malarial parasites are divided into determined species that are not intertransformable is also favoured by the other facts taught by clinical experience,the geographical distribution of the various kinds of fever,the almost exclusive domination of one species in certain localities,etc.The specific nature of the tertian,quartan,and the aestivo-autumnal parasites are the arguments which have been already briefly outlines as demonstrative of our contention. But,while those of the tertian and quartan each represent a species which,wherever tertian or quartan fever exists,occurs with certain determined morphological and biological preperties,whether the same is the case with the aestivo-autumnal parasites is a question - i.e.,we must enquire if the parasites which we have described as aestivo-autumnal represent one individual species, or if they include various species and varieties.The question is still,however,an open one.Considering that in the groups of fevers bound to the biology of this parasite there are two fundamental clinical types,- viz.,the aestivo-autumnal tertian,which is the predominant and most important,and the quotidian,- we must endeavour to ascertain the morphological and biological differences which exist between the parasitic forms found in cases of typical aestivo-autumnal tertian,and those which in cases of quotidian are to be observed. The morphological and biological differences in question relate to five points - viz.,the duration of the cycle of development,the pigmentation,the size of the parasite,the amoeboid movements,and the duration of the various life phases in relation to the febrile cycle. Let us briefly consider these:The duration of the cycle of development,which in the quotidian is completed in about twenty-four hours,in the tertian is completed in about forty-eight hours - according to the most modern researches. In adult forms of tertian the pigmentation is more abundant,and sometimes endowed with oscillatory movements,which in the quotidian are never observed. The size of the parasite at the same stage of development is greater in the tertian parasites than in the quotidian;in the former even the fission forms are of greater dimensions.In the tertian the motility is preserved for a longer time;even in the pigmented adult

bodies the movements are more active,and the amoeba tends to assume various and grotesque shapes from the rapid emission and retraction of the pseudopodia.The movements in the pigmented stage are less active,and of shorter duration,in the case of the small amoeba of the quotidian.Regarding the last-mentioned point,- the duration of the various life phases in relation to the febrile cycle,- the duration of the non-pigmented amoeboid form is very long,and may even go beyond twenty-four hours.Moreover,the forms of the young generation in the summer tertian usually appear in the blood several hours after the beginning of the attack - much later than those of the quotidian,to put it differently.The resemblances,in spite of these differences,are so great as to render a differential diagnosis very difficult;all these parasites affect the red blood-cells in the same way,all possess a life phase represented by the crescent forms.Therefore,one may reasonably enquire if these parasitic varieties are such in the true sense of the word,or if it is one parasite which exhibits great variability in the duration of its development,so that between the two extremes (twenty-four hours in the quotidian,and forty-eight hours in the tertian) these are all the intermediate grades.It would be easy enough to ascribe the morphological differences to the varied duration of the life cycles if we were to hold to this view. The Haemamoeba immaculata - the parasite which completes its whole life cycle without becoming pigmented - probably represents a species or variety by itself of the aestivo-autumnal parasites.But,in the present state of our knowledge the question cannot be definitely answered in relation to these parasites.Recent facts learned in investigation of the life cycle of the malarial parasite in mosquitos give support to the opinion that the malarial parasites represent distinct species. These researches permit us to dwell upon the question of the difference of species only with reference to the aestivo-autumnal and the ordinary tertian parasites;for observations are as yet incomplete with regard to the life of the quartan organisms.According to Bignami and Bastianelli,the tertian sporozoon in the anophelic life is to be distinguished from those of crescent origin by the morphological characters,hereafter to be given;the young bodies chiefly distinguished by the form of the sporozoa and the character of the pigment;the forms undergoing development by the size of the little bodies successively produced by the division occurring in the nucleus.In general,the size and disposition of the so-called residua of segmentation will serve for the distinction of the adult forms with sporozoites.These facts are borne out by the studies of various observers. Indeed,is we nourish mosquitos with blood containing crescents,and after these have completed their whole life cycle up to the infection of the salivary glands with sporozoites,cause the same mosquitos to bite a healthy person,an aestivo-autumnal fever will develop. This experiment has been made,by the two authors above-mentioned,in the winter - a season in which the anopheles taken in a free state did not give aestival fevers, but,when they produced fever at all,caused the ordinary tertian.They both affirm that in the mosquito the distinction between the species of the malarial parasites does not undergo any change.

We shall now consider in detail each of the varieties of the parasite of malaria.

PARASITES OF QUARTAN FEVER.

In the majority of malarious regions these are the rarest form of the malarial parasite; but there are certain places where it is the prevailing variety. Being particularly common in the neighbourhood of Pavia (Italy), the quartan parasite was the first to be differentiated and described by Golgi (1885-86). In the case of the quartan parasites there are two life cycles to be distinguished - one being completed in man, the other begun in man and completed in certain mosquitos. The bodies of the first cycle are well known from Golgi's description (Arch. per le Sci. med., 1886); those of the second cycle are not so generally known as the corresponding ones of the tertian and aestivo-autumnal germs. The life cycle which is completed in man develops in a period of three days - i.e., in the interval between two typical quartan attacks - and is intimately and regularly related to the occurrence of these attacks; in fact, the onset of a febrile attack coincides with the stage of multiplication of the parasites. The whole development of the parasite up to sporulation may be easily followed in fresh preparations made during a quartan attack, and during the two days of apyrexia between this and the next attack. No phase of life escapes the observer, because development occurs in the circulating blood; while in the case of the aestivo-autumnal parasites the adult and multiplying forms accumulate in the internal viscera, and even the tertian parasites show a tendency to accumulate at the same stage in the vascular area of the spleen, although not to such an extent as to prevent in the peripheral blood their entire development being followed. Less motile in character and less transparent in appearance are the young parasites, which occur as small endoglobular amoeboid bodies without pigment, exactly similar to the tertian bodies but for the distinction named. They appear in the blood during the febrile attack, and rapidly become pigmented - so much so that on the first day of apyrexia we find in the blood endoglobular pigmented parasites, about one-fifth or even one-quarter the size of the red blood-corpuscle, and endowed with torpid movements, as shown by the slow change in shape of their outlines. The red cells containing them are normal in size and appearance. During the whole period of apyrexia the parasites slowly increase in size, preserving the same appearance; their movements become gradually slower, so that they do not tend to assume the irregular and grotesque shapes taken by the tertian parasites, but remain more or less round. As the parasite grows, the pigment becomes more abundant, and occurs in black granules, which are notably larger than in the tertian parasites, and usually non-motile. The red cell preserves its normal size, or, if at all modified, tends to be somewhat smaller; its substance is gradually replaced by the parasitic body which is developed within it; but around the latter there persists, up to the point of complete development, a sort of ring of substance coloured by haemoglobin: indeed, even darker than normal may be the haemoglobin colouration of the residual portion of the red blood-corpuscle. On the other hand, the adult forms are round,

pigmented bodies,almost as large as a red blood-corpuscle,which have invaded the whole(nearly) of the containing corpuscle,of which only a slender zone around the parasite still persists.We see others along with these forms in which there is apparently no trace of the red blood-corpuscle;but,representing the peripheral residuum of the invaded cell,a very thin involucrum will be discovered in closer examination.From eight to twelve hours before the febrile attack,whose onset corresponds with the end of their life cycle,these bodies,- which have attained the maximum growth of quartan parasites, and in whom we can see the first indications of the internal changes which lead to fission or sporulation,- are found in the blood.In the course of the last eight to twelve hours,and in fresh specimens,some of the phases of segmentation may also be followed,and are the first stages of the process;on the other hand,we find that nuclear division begins first in the adult pigmented bodies,with irregularly disseminated pigment,in the case of preparations properly stained.In fresh preparations,what happens is that in the adult forms the pigment tends gradually to accumulate at the centre,where from the beginning we find the pigment irregularly arranged in striae or trabeculae,or sometimes in striae radiating from the centre to the periphery of the parasitic body;then the pigment which forms the striae gradually gathers towards the centre,forming a globular mass with well-marked outlines.At the same time the parasitic body shows a line of division,which little by little becomes more distinctly visible.The formation of from nine to twelve pyriform or ovoid bodies,which arrange themselves around the central mass of pigment with remarkable regularity,is the result of all this and the final one. Continuing to observe under the microscope one of these segmented forms,we often see the small pyriform or oval bodies,which have arranged themselves in wreath form, take on a more globular appearance,become slightly displaced and pushed away from each other;and then,when the thin involucrum formed by the red blood-corpuscle has disappeared,they appear simply as little masses of free,rounded bodies near the residual block of pigment, their original regularity of arrangement being lost. The sporulation is broken up at this point,and new fed blood-corpuscles - in which they begin their regular life cycle - are invaded by the individual gymnospores. The same regularity is not always seen in connection with the occurrence of sporulation - more especially in relation to the deposition of the pigment,which may collect in two or more masses,or remain in an irregular fashion between the bodies resulting from fission,instead of being centrally or subcentrally situated in one mass.But these details are of no importance.Of more interest,however,is the fact that sporulation may occur in bodies which have not attained the size of normal adult parasites,but which are decidedly smaller than the corpuscle containing them,of which as much as a third may persist.In the other species of parasites,the size of the adult bodies in segmentation may vary between wide limits.In this respect,indeed,the quartan parasites show more regularity than do others.The quartan parasites corresond in structure with that of other species.

The young and the developing forms have a pigmented cytoplasm,and a nuclear formation consisting of a little boby of chromatin surrounded by a pallid zone.The line of demarcation between the clear zone - nuclear juice - and the cytoplasm is very distinct.In the advanced stage of development the chromatin,instead of being gathered into one deeply stained body,is arranged in rods and filaments.The segmentation of the nuclear chromatin, by which the nucleus divides into two,four,etc.,occurs in the same way as in connection with the tertian parasites.In bodies in which we witness the splitting-up of a mass of chromatin into two parts,we see the mass assuming orregular and dentilated outlines,showing probably that it is made up of small filaments of chromatin. Around the individual masses of chromatin resulting from the successive divisions,the pallid zone is always visible,although it is thinner and has less distinct outlines than in the young forms.The individual gymnospores are composed of a cytoplasm which stains a deep blue, and of a small concentrically situated body of chromatin (corresponding to the shining spot seen in the spore in fresh preparation) of compact appearance,but without recognisable structure.This structure,in all essential points is the same as that of the quartan parasites. According to Grassi and Feletti,the young quartan parasites which have just entered into a red corpuscle consist of a relatively large,excentric nucleus,surrounded by a scanty cytoplasm,and furnished with a delicate membrane,containing the nuclear juice and the so-called nucleoliform node,which represents the chromatin substance of the nucleus and lies close to the nuclear membrane.The cytoplasm may possess an alveolar structure. With the development of the parasite the cytoplasm grows more than does the nucleus;and when the haemamoeba has reached a certain size,we often note the appearance of filaments which unite the nucleoliform node to the nuclear membrane;the node and the filaments represent the so-called nuclear reticulum.Later the nucleoliform node increases in size,and then divides into four,five, eight,ot ten little nodes,each of which becomes surrounded by nuclear juice and a very deliacte membrane.What becomes of the reticulum and nuclear membrane during multiplication the authors quoted above have not been able to ascertain.The amoeba thus becomes multinuclear. Later,- and the process is held to indicate that the haemamoeba is reproduced by direct division of the nucleus,- a little cytoplasm forms around each nucleus, and thus is formed the complete gymnospore.Nevertheless, it would appear that multiplication occurs by a rudimentary form of karyokinesis,not by direct division of the nucleus;and,furthermore,we do not see the nuclear membrane,whose presence can at the most be merely deduced from the distinct line of separation of the clear zone from the cytoplasm,nor do we see the nuclear reticulum from the nucleoliform node,etc. Now,regarding the forms which begin in man the cycle completed in the Mosquito,as is also the case with the cycle of the quartan parasite in that insect,these are but little understood.We can see adult forms,which take up nearly the whole of the substance of the red blood-corpuscle, which have irregularly disseminated pigment and abundant

nuclear chromatin arranged in threads or rods.As in these forms,no matter how large they grow,we see no sign of division of the nucleus,while in bodies of equal size which end in sporulation the nuclear division is already well advanced,that they remain sterile in man,and are analogous to the large pigmented tertian forms which are also sterile in man,is a natural supposition.These adult bodies,undergoing degenerative processes similar to those of the tertian,are to be seen in fresh preparations.It is a well-established fact that the quartan parasites may give rise to flagellated forms;yet,according to the experience of many, it is rare to find this phase of life.While the patient investigation of a case of aestival or of tertian infection is sure to be successful,at a given period of the disease,with a view of the forms known as gametes, and of the flagellates especially,we may follow the course of a quartan for weeks without finding even one. The first to speak of flagellate quartan bodies were Bastianelli and Bignami,- the biological significance of which,reasoning by analogy,is that it is the same as that of similar bodies of eastival and tertian parasites;and Thayer and Hewetson,who found them in two out of five cases,describe them as smaller than those of the tertian,and as differing in the nature of the pigment which is found in the body from which arise the flagella, the pigment granules being larger and blacker.The movemnts of the flagella are apparently not slower than in the tertian.According to the same authors,on the whole, the quartan flagellated body resembles not those of tertian origin,but rather those of aestival.

PARASITES OF TERTIAN FEVER.

In connection with the tertian parasites also there are to two life cycles to be considered - one of which is completed in man,while the other begins in man and is completed in some species of mosquito.In most malarious regions this variety of the malarial parasite is common.Where only mild types of malaria occur it is, as a rule,the prevailing,and sometimes the sole,variety observed.The tertian and the quartan parasites cause most,if not in some places all,of the winter and summer intermittents;but they,and especially the tertian parasite,may cause in districts of even severe malaria not a few of the malarial fevers of summer and autumn,although the more severe and irregular of these fevers are caused chiefly by the aestivo-autumnal organism. Still, severe as well as mild types of malarial fever may be produced by the tertian parasites.The phases of development of this parasite was differentiated from the quartan,and described in its essential characteristics by Golgi in 1886 and 1889.His first description has been added to,and in some points corrected,by Antolisei (1889-90) and Bastianelli and Bignami (1890),and other observers.The analogy with the crescent forms was proved by the two last-mentioned investigators.The life cycle which is completed in man is in intimate relation to the successive febrile attacks;and the duration of this cycle,from the youngest forms to sporulation,is about two days.The time which elapses between the beginning of one attack and that of the next one is its equivalent.The tertian parasite becomes larger than a

normal red blood-corpuscle during the course of its development - that is to say,much larger than an adult aestivo-autumnal parasite,from which it differs not only in size but in appearance,in the nature of the pigment, of the sporulation,etc.The two species possess essentially the same structure;but the differences in pathogenic action between the two is well-known.Under the microscope it is very difficult to distinguish the young non-pigmented forms from those of the aestivo-autumnal,as they are so similar.They are usually a little larger,however,and less opaque.They are very motile,and go through the usual changes in form - passing from the discoid to the annular form,and from this to the amoeboid.The forms in motion send out slender prolongations - pseudopodia - which may ramify in every direction,sometimes reaching the periphery of the red blood-corpuscle,but not going beyond it.The most varied and strange forms imaginable result from the fact that they also then retract,and other similar pseudopodia project from other parts of the parasitic body.In the tertian parasites pigmentation occurs with rapidity,while the similar non-pigmented pase in the aestivo-autumnal is of long duration.The pigment in the initial forms is scanty,and in very fine granules,and has a tendency to accumulate at the extremity of the pseudopodia.The structure of the young forms is like that to be described in the aestivo-autumnal parasites; in properly stained preparations they are seen to be formed of cytoplasm which is stained - in Romanowsky's method - blue,against which is seen the chromatin body stained purplish-red,round or ovoid in shape,and larger than is is similar body in the first stage of development of the aestival parasite.We see around it a slender pale zone,which separates the chromatin from the cytoplasm;though we do not always see it in the aestival parasites,except at a stage more advanced,it is constant in these forms.We see only the parts just mentioned in many endoglobular parasites,and in those which are free in the plasma.But in other endoglobular parasites we may find the characteristic ring - that is to say,a blue ring which is,as a rule,thicker in one-half than in the other,enclosing a space which is of about the colour of the red cell,or a trifle lighter.At one point of the periphery of the ring we find the nuclear formation mentioned - that is to say,the chromatin body surrounded by a pale zone.In these forms it is readily seen that we have not to do with a larger vesicular nucleus occupying the whole centre of the ring,but with a vacuole from which the limiting outline of the clear zone serves to distinguish the nucleus embedded in the cytoplasm. The most varied forms are to be seen is the parasite be fixed during amoeboid movements.The round or roundish vacuole is usually found near the nucleus;and from the surrounding ring of protoplasm we see simple or ramified prolongations projecting,which are sometimes very long. Other non-vacuolated forms may have the shape of a horse-shoe,or of a slender filament of cytoplasm (the nuclear body being situated near one of the ends of this,or even at its end) curved upon itself in various ways. The special characteristics of the tertian parasite are more in evidence in the forms of more advanced development.

The increase in size,- which is due chiefly to the growth of the cytoplasm,there being no proportionate increase of the nucleus,- is very marked,so much so that in the first twenty-four hours the parasite may take up from one-half to two-thirds of the red corpuscle. The parasite appears to have acquired more definite outlines in a fresh preparation;it contains many granules of melanin,and possesses lively amoeboid movements,which cause it to assume curious shapes within the corpuscle. Even when the movements of the cytoplasm are not shown by marked changes in the outline,we often see the pigment granules change place,sometimes slowly,but usually with great rapidity,looking very like the darting of flies.This motion is believed to be due to the plasmatic current,like which it is more or less rapid;it is not trembling in character,neither has it the regularity of a Brownian movement.That the parasite-containing red blood-corpuscles are markedly larger and paler than normal is one of the most striking facts;indeed,the rapidity with which swelling and decolouration of the infected red cell occursis one of the most characteristic properties of the tertian parasite.During the second twenty-four hours the development of the parasitic body continues until it is about two-thirds to four-fifths the diameter of the enclosing corpuscle,which is usually the limit of growth of the adult body.With the exception that the amoeboid movements are a little less rapid,- for which reason it is apt to maintain a more or less rounded form,and does not assume the bizarre shapes seen in the younger stages,- in this last period of development it maintains the characteristics already described.What has already been said applies to its structure also.Nevertheless,the chromatin is a trifle less deeply stained than in the very young forms;and, according to Romanowsky,it appears to be composed of very fine filaments and points,which latter probably represent the cross section of the filaments.The cytoplasm - stained blue - is found to have increased proportionately more than the nucleus,and is markedly pigmented.The pigment naturally does not invade the clear zone which surrounds the nuclear chromatin,and which belongs to the nucleus - nuclear juice.The protoplasm is stained blue,but the colouration is not always uniform, the difference in thickness of its various parts caused by the amoeboid movements probably accounting for this.In the forms which are as large as half the red corpuscle,we see a vacuole often in the cytoplasm which may be near the nucleus or at the periphery.;there may even be two or three vacuoles.The form of the vacuole is not always circular,but often irregular,and not infrequently prolongations from the cytoplasm may be seen within it;these are evidently pseudopodia that were surprised and fixed during motion.The chromatinic part of the nucleus is seen more clearly than in the preceding phase to possess a fibrillary appearance in the round and but slightly motile adult forms.On arrival at the stage of development,those changes begin which lead to sporulation.The latter,as in the case of the aestivo-autumnal parasite,coincides with the onset of the febrile attack,and is completed within the corpuscle after about forty-eight hours.Scarcely anything of the

interior changes which produce fission are seen in fresh preparations;we see the pigmented body in the process of dividing,or already divided,into daughter bodies - that is to say,only the result is observed. Golgi - in view of the very varied forms seen in fresh preparations - recognises several methods of segmentation in the tertian parasite.The most frequent occurrence is to see adult pigmented bodies,in which the pigment is more or less entirely collected in the centre;around this pigment mass the parasitic body divides into a varying number of little spheres,- about fifteen to twenty,- which all together form a round mass.They do not essentially differ from those forms in which the pigment,instead of remaining at the centre in one mass, is found at the periphery,or is divided into two or three small clumps,or is irregularly disseminated betwe-en the individual bodies.The same author affirms that the segmentation in other parasitic bodies may occur in a very different way,namely,by the formation of figures resembling sunflowers.According to him,when the pigment is gathered at the centre of the parasitic body,the peripheral portion of the latter appears to separate itself from the pigmented centre in the form of a ring. In this ring radiating striae very soon appear,which at first are scarcely visible,but gradually become more and more marked,and which subdivide the ring into numerous portions composed of a whitish substance;these subdivisions gradually become individualised,so to speak, acquire definite outlines,and form so many little spheres which become detached from each other,and finally arrange themselves in the form of a wreath around a central pigmented disc.Out author regards this as the form of segmentation as most characteristic of the tertian parasite,and the one differing most from the fission process of the other forms of parasite.He also indicates a third method of segmentation seen in free bodies,but does so somewhat doubtfully.In these bodies we occasionally,he says observe that the "pigment,instead of being masses at the centre as usual,gradually becomes arranged in a zone more or less close to the periphery,this occurring in such a way as to determine a somewhat distinct line of separation between the part occupied by pigment and that which is free from it.The latter becomes exceedingly transparent,sometimes appearing like a vacuole,within which may be seen one,or more rarely several,spheres similar to those which result from segmentation" Nevertheless,later studies on the structure have shown that this is not a process of multiplication by segmentation but of degeneration, which occurs in the large pigmented bodies free in the plasma.The various changes described above,which may be witnessed in fresh preparations,in the fission forms occur with great rapidity at the onset of the attack, and represent only the latest phases of fission.During the microscopical examination all that we are able to see is the more or less rapid separation of the daughter bodies from each other;but in blood taken from the circulation,that is to say,in the ordinary preparations, the various phenomena leading to the formation of the individual parasites cannot be followed.The fact that the gradual passage of the uninucleated adult body to a comparatively completely segmented form occurs in successive stages with marked slowness,- the process

sometimes taking more than twelve hours,- is demonstrated by an examination of stained specimens, especially those made after Romanowsky's method. This is fundamentally the same process as that described later in connection with the aestival parasites; but, because of the greater size of the tertian parasites, it can be more clearly observed. The nuclear chromatin, as we have already seen, in the adult forms presents a less uniform and compact appearance than in the young forms. When the stage of division approaches, the filaments or rods, which give a lenticulated appearance to the chromatin mass, tend to separate, leaving clear spaces between them, so that the nucleus becomes two or three times larger than in the young forms. At the same time, the pale zone surrounding the chromatin becomes thinner and less easily distinguished than before from the surrounding protoplasm. The chromatin now divides into two masses, which sometimes take on the shape of semicircles, whose concave surfaces face each other, and are then transformed into more or less compact masses, surrounded by a narrow clear zone. We have thus two new nuclei, somewhat smaller than the original nucleus. From this, by a similar process of division,- with each act of which the clear zone surrounding the chromatin becomes less visible, but again becomes more distinct again after the formation of the new nucleus,- are formed other nuclei, which having a tendency to separate from each other arrange themselves towards the periphery of the cytoplasm. This clear zone is never invaded by the pigment. The latter gathers in one or more clumps at the periphery or at the centre of the parasite, being pushed away by the successive divisions of the nucleus. Pigment bodies with two, four, six, or more nuclei are formed by these successive divisions, which also lead to the formation of from sixteen to twenty nuclei, which is the average number of spores to which a tertian body gives rise. In preparations made about six hours previous to the febrile attack,- which coincides with complete segmentation,- one may observe pigmented bodies with about eight nuclei, more rarely ten or twelve. When the process of formation of daughter nuclei is finished, a portion of the cytoplasm condenses around each, becoming separated from the surrounding parts; thus is formed the daughter body,- spore or gymnospore,- which is therefore composed of a small mass of strongly stainable chromatin, surrounded by a narrow clear zone, and by a ring of protoplasm which is of a deep blue colour. A portion of the cytoplasm, which is less deeply stained and which contains granules or needles of black pigment, remains unused and is called the residuum of segmentation. As a rule, the nucleus is excentrically situated in reference to the cytoplasm. The red corpuscle, which in fresh specimens has become almost invisible from the gradual consumption of the haemoglobin, at this point bursts open, possibly by reason of the swelling of the part of the protoplasm which represents the residua of segmentation, and the gymnospores become free. The diversity of the contradictory results obtained by other observers than Romanowsky, Ziemann, etc., whose idea of the process of fission has just been given,- is due to varying technical methods which they employed. Mannaberg, by staining with haematoxylin, was not able to observe the successive divisions of the chromatin, for which reason

he believed that the chromatin,- nucleolus,- in forms about to divide, came out from the nucleus and mixed with the cytoplasm; therefore, the stage in which the parasite is preparing to sporulate he considers to be characterised by the disappearance of the nucleolus (nuclear chromatin, nucleoliform node). But this disappearance in the case of the aestival parasite does not exist. The error probably arose from the fact that there is a phase in the life of the parasite in which the nuclear chromatin cannot be distinguished by the depth of the staining,- haematoxylin method,- from the cytoplasm, and this is precisely the stage in which the chromatin undergoes successive divisions. Now, regarding the forms which begin in man the cycle which is completed in the mosquito, it may here be noted that for a long time observers had perceived in the tertian blood, in addition to the pigmented bodies which, when they reached the adult stage, underwent the modifications described up to sporulation, there were others which, although they grew even larger at first, did not become segmented but underwent other transformations. In other words, they in part fell a prey to various degenerative processes, and in part flagellated. Celli and Antolisei looked upon these bodies - which they first described - as forms of degeneration. Their analogy to the crescent bodies was demonstrated later by Bignami and Bastianelli, who also held that here, as in the aestivo-autumnal species of the parasite, their significance is the same. In fresh preparations, in their adult form they are seen as round or somewhat elongated bodies, sometimes with a long diameter twice the size of that of an ordinary red blood-corpuscle; the red cell containing them is, of course, enlarged and pale, sometimes even entirely decolourised. The protoplasm contains a large amount of black or brick-red pigment in most active motion; and sometimes there may be found a somewhat large hyaline vesicle, usually excentrically situated, and evidently representing the nucleus. This is perhaps the only form of the tertian parasite in which the nucleus is visible in a fresh preparation without any staining; and it is likely that there is a nuclear membrane which is not visible in the stained parasites, as this nucleus has a distinctly vesicular appearance, and a decided outline which the pigment - in spite of its motility - never goes beyond. Continuing to observe one of these bodies, we often observe that at one particular point a small transparent sphere is formed and around it a vacuole, then near to the first one other spherules and vacuoles appear, until the whole parasite has been converted into a mass of globules of varying size, between which are disposed the pigment granules, whose oscillatory movements cease entirely. Sometimes while this vacuolisation and progressive splitting of the parasitic body into hyaline spheres is taking place, a part of the cytoplasm projects beyond the red blood-corpuscle; and until this portion also is broken up into hyaline masses the oscillations of the pigment continue. Both Celli and Antolisei were well aware that this process of disaggregation and vacuolisation indicates the death of the adult parasitic body. The description given by some writers of reproduction with vacuolisation of the tertian parasites - a reproduction whose various phases can be followed by microscopical examination - corresponds perfedtly to

the phases of this degenerative change.The fact that sporulation always occurs in the characteristic manner described above that it is not a multiplication. During the time that some of these bodies are seen to become vacuolated and to divide into small transparent masses of unequal size,or to present both phenomena at once,others during the microscopical examination suddenly exhibit a confused movement of the cytoplasm and of the pigment contained in it,and then - in precisely the same way as the round bodies belonging to the crescent stage become changed into flagellated bodies - become converted into flagellated bodies.From the pigmented masses small hylaone buds are seen coming which give rise to flagella.When the movement of the flagella ceases and they have become detached and removed from the pigmented body,a sort of clot of pigmented protoplasm remains behind,and then divides into a variable number of transparent spherules.Soon after this all movement in the pigment ceases.The pigmented bodies,- those which become flagellated as well as those which do not,- in preparations stained by Romanowsky's method are seen to be composed of an abundant amount of cytoplasm which is stained blue;a vesicular nucleus,which contains threads or granules or rods of chromatin surrounded by a clear zone,is also present. Now,when these bodies remain in man they end in degenerative processes,and are taken up by the phagocytes,as occurs in the bodies of the crescent group.In fact,in the examination of stained specimens we find a few which contain very little chromatin,or none at all - sterile bodies as they have been termed.But when,in their adult stage, they are taken in with the patient's blood by the mosquito,they develop in the intestine of the latter,provided it belongs to the right species.Like the crescent forms,they are held to be gametes;for their biolcgical significance is identical.Their development has not been followed as completely as that of the crescents;still, in preparations made after Romanowsky's method,Bastianelli and Bignami have observed parasitic forms about half the size of the adult bodies described,which are distinguished from the forms of the first cycle multiplying in man by the nature of the nuclear chromatin.Their chromatin is arranged in threads and rods, sometimes forming a sort of reticulum,and neither so compact nor so deeply stained as in the forms capable of sporulation.These bodies are probably forms of gametes in processs of development.We cannot tell if the youngest forms are present in the bone marrow,as in the case of the young crescents,by direct examination.It is believed by many that these large pigmented bodies represent the gametes of the tertian parasites;and the reasons for this belief are the same which have been given in the case of the crescent forms,that is to say, reasons based upon morphological studies and upon analogy.It follows that these parasitic forms,like the crescents,should be divided into two classes,namely, the macrogametes or those which do not become flagellated,and the microgametocytes or those that do.Preparations of tertian blood,kept in a moist chamber for twenty minutes and dried and stained by Romanowsky's method,will suffice for the demonstration of the differences between the first and second.We find the

nucleus in the firstmto be somewhat swollen and situated at the periphery of the protoplasm.In the second,or microgametocytes,the nucleus is at the centre of the parasite;and it contains a larger amount of chromatin,- five or six times as much as in the macrogametes,- which is gathered in apparently a single mass at the centre of the nucleus,or as deeply stained intertwined threads.From these bodies arise the flagella - microgametes - by a process which,to judge from the transitional forms,may be described as follows:The chromatin (all of this being used up in the formation of the microgametes) divides into a number of small masses which are carried to the periphery,each mass then becoming transformed into a filament which projects from the parasitic body,and is surrounded by a thin layer of protoplasm.The above description of the flagellata of crescent origin does not exactly apply to these tertian pseudo-flagellata;for here the number of flagella is usually greater,- as a rule,they contain six,- and in their entirety they are larger.The formation of the microgametes in their normal surroundings,the middle intestine of Anopheles,occurs in the same way.The fecundation of a macrogamete by the entrance of a flagellum appears to take place in this locality.The tertian parasites will already be found in a condition to develop in the mosquito if a patient suffering from primary tertian infection be stung a few days after the beginning of the disease.The further development of these bodies,which are already found at an adult stage in the blood of patients with tertian fever a few days after the onset of the infection,has been already described.

PARASITES OF AESTIVO-AUTUMNAL FEVER.

The small protoplasmic bodies(which are found either adherent to the surface of the red blood-corpuscles or in a sort of niche on their surface or edge or else within their substance - non-pigmented plasmodia or amoeba of Marchiafava and Celli) represent the young forms of these parasites.They may be endowed with lively amoeboid movements,or immotile - discoid and annular forms.The endoglobular forms are those undergoing development;and we find in them very fine granules of black or brown pigment arranged,with more or less regularity,at the periphery of the parasitic body (forms with pigment granules);these may move like small amoebae or be immotile (discoid or annular).The pigment at the periphery of the parasite,in the more advanced stages of endoglobular life in which the parasites are preparing to multiply,shows a tendency to gather at one point at the centre or slightly eccentrically (forms with blacks of pigment) or in one block or in a thick mass of black graules.While the young non-pigmented forms,as well as those in process of development,are found circulating in the peripheral blood,the bodies with blocks of pigment are found accumulated in the vascular system of the viscera,- spleen,bone marrow,brain in cases of pernicious fever,etc.,- excepting in very grave infections,in which they may be found in the circulating blood.One of the most important characteristics of the aestivo-autumnal parasites,as distinguished from the other species,is constitutes by this distribution of the various parasitic forms in the vascular system.The parasitic body,in the forms with blocks of pigment,divides into a variable

number of round or ovoid bodies,all alike and of the same size,which arrange themselves usually in a single or double wreath around the pigment.This segmentation which occurs within the red corpuscle,whose size the parasite does not attain even at its most advanced stage of growth,constitutes the mode of multiplication of the parasite in man (fission or sporulation forms). In the vessels of the viscera these forms are found stationary,like those of the preceding stage.New red corpuscles are invaded by the little bodies resulting from fission,and they recommence the life cycle just mentioned.Because of its intimate relation to the development and succession of the febrile attacks,these successive phases of existence constitute the human cycle of the parasite,or,as it has also been called, the pyrotogenous cycle.It is not,however,in this way that all the parasitic forms develop.In all cases,a certain number of young pigmented bodies continue to grow and become ovoid or spindle-shaped,while the pigment increases in amount and takes on the appearance of needles or little rods.One will usually observe a curving into a crescentic form,- body No.1 of Laveran, crescents,ovoid,and fusiform bodies,- when these fusiform or ovoid bodies by their increase in length have become longer than the diameter of the red corpuscle in which they have developed.In ordinary fresh preparations,if observation be continued for some time, these bodies,which begin in man the life cycle which is continued outside of the human body,are seen to present certain important life phenomena.After ten minutes,or even more,we see that while certain of the crescents persist in their typical form,others become ovoid and then round.Then in the round bodies,- the biological significance of which can only be understood by following the later phases of development in the mid-intestine of the mosquito,- there begins an active movement on the part of the granules or rods of pigment,followed by the tumultuous thrusting forth of several filaments, usually four,which move like flagella.They usually become detached and continue to move with the greatest rapidity among the red corpuscles (body No.2 of Laveran,flagellated body of the majority of writers). In the crescent phase these forms represent the beginning in man of a cycle of life which is continued and completed in the mosquito.Unlike the forms of the first cycle,they have no pathogenic action in man;and because their development has been seen only in some species of mosquito belonging to the genus Anopheles, they have been termed forms of the anophelic cycle. To commence with the bodies of the pyrotogenous cycle,- i.e,,the young non-pigmented parasites or the non-pigmented plasmodia of Marchiafava and Celli,- we may note that these forms,seen in fresh preparations,occur as small whitish protoplasmic masses,possessing rapid amoeboid movements,which take place at the ordinary temperature of the atmosphere from July to October,and are quicker than those of the leucocytes at the same temperature.In a state of rest they are discoid in shape;from this form they pass to the most varied shapes,such as stars,crosses,and other odd forms,pushing our slender,diaphanous prolongations which oscillate in the substance of the red cell;they sometimes

even ramify,and then become retracted while new ones are pushed out at other points of the periphery.After a while they become round again.At the ordinary summer temperature these movements may continue for from twenty to forty minutes,sometimes as long as five hours. When they have ceased,or are about to cease,they can be revived by using the warm table,and by passing through it a current of water at 102° to 104° F.Sometimes the little body moves as if it were about to emerge from the corpuscle,but its pseudopodia never go beyond the limits of the red cell.When it stops moving it takes on a circular form,which is wtiter at the periphery than in the centre (discoid form).Careful observation of one of these discoid forms shows that the central part gradually becomes differentiated more and more from the periphery;little by little it loses its whitish aspect, and through it can be seen the haemoglobin of the red corpuscle;the periphery,on the other hand,becomes more distinct and of a shining white,as if it were thicker.Thus is formed a distinct ring,which looks as if it were printed in the red cell (annular form);and this is a more prominent form than the preceding one,by reason of its greater refractive power.The aspect of these small rings may be seen to undergo alteration;the cytoplasm which forms the ring spreads towards the centre which resumes its whitish diaphanous appearance,and it also spreads peripherally,the parasite thus becoming larger and of a more uniform appearance.It gradually returns to its discoid shape,which is larger than the ring from which it starts,and into which it may again become changed.Amoeboid movements,but slower than before,may again be observed in connection with the ring which has become discoid.By examining one parasite only with a homogeneous one-twelfth immersion lens,this succession of forms - amoeboid,discoid,and annular - may be easily followed. It was by this means that these little bodies were seen and described by Marchiafava and Celli who,having at first limited their investigations to primary cases of grave aestival infection,- which seemed to lend themselves most readily to the study of the malarial parasite,- were led to attribute the greatest importance to these little bodies.In these cases,in fact,the above-mentioned bodies are those which chiefly attract the attention of the investigator;and the strongest impression of a living being is given by this,amongst all the forms assumed by the malarial parasite,by its special characteristic of motility.When in a state of rest (discoid form) these yuung forms closely resemble discs,that is to say,they are so flattened that their lesser diameter corresponds to the thickness of the red blood cell.This is seen obliquely in the rare cases in which the little amoeba turns upon itself,but very often when it is endwise presented to view.An estimation of the true significance of the annular bodies is a matter of much more difficulty. Marchiafava and Celli held that the so-called rings, which are so plainly seen as if printed on the red corpuscle,were merely amoeboid bodies which,becoming very thin at the centre,allowed the central part of the corpuscle to show through them;by this thinning of the central portion and consequent thickening of the peripheral zone,there is formed a biconcave lens-shaped figure,

somewhat resembling the corpuscle itself.In fact,if we observe one of these ring-shaped bodies when it presents itself endwise,- which,as we have seen is rare,but still may occur,- we have actually the impression of a biconcave lens.Antolisei,who though t that from the absence of analogous facts it was highly improbable a living orgamism could take on such an appearance,held that the annular forms were merely small amoebae which had included in their substance a small particle of the red cell,as Osler and Councilman first suggested.Taking into consideration the way in which a discoid form is seen to become annular during the microscopical examination,one can hardly accept Antolisei's view.Were it correct,we should see the amoeboid parasite,when about to become annular, lengthen itself like a rod,then curve like a horseshoe, and finally unite the two pseudopodia after having included a portion of the red cell - in fact, the thing would have to occur as it does when an amoeba or a leucocyte invades a foreign body. The fact,however,that it occurs in an entirely different way has already been demonstrated. There are many who assert - and there seems no reason to doubt the hypothesis in question - that the annular form represents a parasite with a central vacuole,around which the substance of the amoeboid body arranges itself in ring form.It is easy to understand why,in the examination of a fresh ring specimen,the ring seems to be entirely absent at the centre,and,seen endwise,it has the appearance akin to that of a biconcave lens;and this because the vacuole is transparent.It must,of course be distinctly understood that there can be no doubt that there are forms of the annular body which are nothing else than young parasites which have included a portion of the red blood-corpuscles,as Osler,Councilman,and Antolisei affirm.But these must be distinguished from the typical annular forms,which,as can be seen from the description, are merely parasites whose protoplasm has contracted in ring shape around a diaphanous,very transparent substance,which constitutes the vacuole.This vacuole disappears in the bodies of the next phase when the stage of nuclear multiplication approaches.It also is worth remembering that it disappears likewise in the cadaver;indeed,in the cadaver we do not see annular bodies,but only,as a rule, immotile discoid or spherical micrococciform bodies. Annular bodies also disappear from the malarial blood which has been strongly cinchonised.All this leads to the belief that we have to do with a vacuole which,in the nutrition of the parasite in its young stage,is of very considerableimportance and significance.Nevertheless,it is an entirely different manner that the forms which include a particle of the red blood-corpuscle behave.First of all,whether the parasite be immotile or in motion,the included parasite may always be seen and followed,while in the annular forms the vacuole becomes invisible so soon as the parasite alters its shape and puts out pseudopodia. Moreover,in the particle of included haemoglobin we often see brown granules of melanin which have come

from the transformation of the haemoglobin, while nothing like this is ever seen in the central portion of the annular forms; but even before the transformation of haemoglobin into melanin has begun, we can see that the included haemoglobin is of a darker colour than normal, and somewhat resembles brass that is old. Finally, we may see plasmodia with gragments of included haemoglobin in the cadaver, and in strongly cinchonised blood; while in blood under such circumstances, the annular forms are not to be found. The following description applies to the structure of these young forms, as shown in preparations stained by methylene blue or by haematoxylin: There is a very thin ring which is coloured blue or violet, and which is deeper and thicket in one-half than in the other; the ring surrounds a space which takes the same stain as the red corpuscle, especially in its youngest stage, while in the centre of more developed forms the red corpuscle is of a paler appearance than is the outside of the ring; there is therefore in this form a very diaphanous portion of the parasitic body, which prevents a perfect appreciation of the colour of the corpuscle. In the thickness of the stained ring we see one, and not infrequently two or more, very small granules of chromatin, which, treated by Romanowsky's method, are clearly visible against the blue substance of the ring, being stained red or purplish-red. Around the chromatin granules we do not see a clear halo, or the constituent parts of a true nucleus, as we do see - in part at least - in the succeeding phases. We have already seen that the chromatin forms a part of the coloured ring: in fact, in the majority of parasites it is intimately connected with it; in some it seems to project from the ring into the substance of the globule, and in others - but rarely - it is found in the centre, and is not connected with the peripheral coloured ring in any perceptible way. As was pointed out by Marchiafava and Celli, as early as 1883, in cases in which the blood is fixed while the young parasites are in motion, we do not see them occurring as regular circles, but with deformities and prolongations. The appearances just described can be explained in view of the fact that the little body of chromatin represents what is rendered visible by our technical methods of a nuclear formation which is apparently very simple; the blue ring is the protoplasm of the parasite, which includes a central transparent portion - i.e., a nutritive vacuole. In preparations which are properly stained, the aspect of these forms renders them clearly distinguishable from the irregular spots stained by the basic aniline colours which are seen within the red corpuscles - coloured dots and spots, the nature of which has been variously interpreted by different authorities. One not infrequently sees, in the red corpuscles, and in addition to ordinary vacuoles, portions completely deprived of haemoglobin, which may be of various forms: some occur as hyaline rods, some as very small round bodies, as rods curved in a horseshoe shape, and even rods elongated into spindles with a point at the centre or nearer to one or the other extremity, which is about the colour of the red cell, or a little darker; these last are the forms which may be

easily mistaken for the rings.Finally,we may see - but rarely - small shining white rings.All these forms - which resemble the young non-pigmented plasmodia - are not infrequently seen in the blood of patients suffering from various diseases,but more especially from tuberculosis,typhoid fever,pneumonia,and suppurative fevers;as a rule,they are few in number,but in some cases they are fairly abundant.An experienced observer has no difficulty in distinguishing these alterations (the little bodies in question when stained are seen to be devoid of characteristic structure) of the corpuscles from young plasmodia;it is only necessary to see the special refraction of the hyaline bodies,which is much greater than that of the parasites.If we watch the succession of the forms above described,from the annular to the discoid and to the amoeboid,the diagnosis of parasites will be assured.Indeed,confusion is impossible if we continue the observation of the suspected bodies,which may,it is true,like the vacuoles, exhibit slow alterations of contour,and even oscillate as if they were about to turn around on their own axis;but we never see any movements,even faintly resembling amoeboid motility.Regarding the plasmodia with pigment granules,- i.e.,the forms in process of development,- although no black pigment granules are discernible even on the most careful observation,the young parasites just described increase somewhat in size,and begin to show a slight darkening around the contour.Preceding the pigmented phase,are to be seen forms which have included a portion of the red blood-corpuscle,- clearly distinguishable from the annular forms,- which,while under observation,become slowly modified in colour and darkened.The pigmented phase is represented by parasites a quarter or a third the size of the red corpuscle,with very fine granules of pigment,which are usually collected at the margin,but are sometimes scattered within the protoplasm of the parasite.It must also be remembered that in many forms the pigment is only apparently marginal,because the peripheral granules at the border,between the parasitic body and the substance of the red corpuscle,are more clearly seen than the others.Many parasites at the same stage as the preceding are of much smaller size. The pigment granules are for the most part immotile, but they may also sometimes oscillate like the pigment of the parasites in ordinary tertian,especially in the larger forms.These pigmented bodies may take on the same form as those of the preceding phase,or present an annular,discoid,and motile form.The annular forms are smaller than the discoid and motile ones,as though they were contraction forms,and they are capable of returning easily to the motile condition.The discoid forms often have a crenated outline;and the motile forms may take on strange shapes,such as the dentritic. One must be very careful,however,even in this phase,to distinguish the annular forms,properly so-called,from the forms which contain one or more fragments of haemoglobin.The differences are the same as those before described.The first have the appearance of a shining ring,one-half of which is thicker than the other,in

sickle form,with the centre showing the red corpuscle,of proper colour or paler than normal;when they become motile again,they spread out,become diaphanous more than before,and in the central portion take on a colour like that of the periphery of the parasite,but usually fainter.The parasites that hold a fragment of haemoglobin may assume any shape without the fragment becoming invisible;this fragment has a tendency,even when the rest of the globule is of normal appearance, to become brassy, and is darker than the red blood-corpuscle.Until the initiation of the changes which lead to multiplication by fission,the amoeboid movements of the parasites continue to be very active during this phase.By a diminution of motility,and by an increase insize of the pigment granules,and a tendency on their part to collect into groups,the next stage is gradually reached.As the parasites develop,the pigment granules,which at first were almost imperceptibly small,become larger and tend to coalesce into three or four small masses,which them take up an eccentric position:at this stage the parasite is more rarely of the dentritic form just mentioned,but usually becomes discoid.By the usual process of staining,it is evident that the structure is the same as in the preceding stage.The parasites occur in rings,which are readily stained by haematoxylin,methylene blue,etc.The coloured ring,- at the margin of which the pigment is chiefly found,- is not of uniform thickness,but usually falciform,this falciform appearance being even more distinct because of the increased size.In situation and other particulars,the chromatin globule,which is larger than in the preceding stage,is the same.In preparations stained according to Romanowsky's method,this globule, which is coloured a violet-red,appears with great distinctness upon the blue ring of protoplasm.In the more developed forms,we find that it is usually surrounded by a pale zone,which is,as a rule,not visible in the preceding stage;it is not homogeneous,but is composed of filaments and rods of chromatin.From this,then,it it evident that the parasite consists of a little mass of chromatin,- the chromatin sometimes occurring in threads,- surrounded by a halo of a pale substance, both together constituting a nucleus,and of a protoplasm containing black granules,which is disposed in annular form around a vacuole.In the more advanced forms of development,and therefore nearer to the next stage of development,the vacuole is no longer to be found;in this case the parasite consists of protoplasm,which is especially pigmented at the periphery,and of a somewhat large nucleus with distinct outlines,in which is seen clearly the chromatin and the pale substance surrounding it.The latter is probably nuclear juice. The division of the nucleus is the chief characteristic of a stage which consists of parasites in process of division, that is to say,of bodies with central or eccentric blocks of pigment.Divisinn of the protoplasm,with the formation of daughter forms,or so-called spores, follows the divsion of the nucleus,which latter goes on till a variable number of very distinct nuclei have been formed.Now,if we begin with the bodies of the preceding stage,we can follow them as they increase in

size;the pigment also increases in the form of fine granules,which tend to collect into large granules,and finally in a block or clump of granules gathered at the centre of the parasitic body,or else situated eccentrically,or even at a point in the periphery of the body itself;these clumps may be two or three in number,or exceptionally even more,but in this case each one if naturally smaller than the single block which is the usual form.Rapid oscillating movements may be observed in the pigment when it is collected into little granules or rods,or the same may not be capable of any motility.Though the average size of these bodies is about a third of that of the corpuscle, it may vary from a quarter to a half of that of a red blood-cell.But some are so small as not to fill the corpuscle,even when two or three or more of them are aggregated therein.It is in fresh preparations that the structure of these little bodies is best seen;they appear to be composed of protoplasm which is rather highly refractive,and to be homogeneous.At the periphery a series of shing dots - indicative of an advanced stage of the process of division - will be seen in the more progressed stages of development. These bodies are found to consist,- when stained with haematoxylin in preparations dried according to Ehrlich's method,and fixed in absolute alcohol and ether,- of one part which is coloured a deep purplish-blue, usually at the periphery of the parasite,and of another very slightly stained and less extensive than the first,which corresponds with the pigment.In many of these bodies the mass of chromatin cannot be made visible by this method,which circumstance has suggested to some that it is dissolved and mixed with the protoplasm.Towards the periphery of the stained portion of the protoplasm, a variable number of minute bodies,of a more intense blue colour,which represent the chromatin bodies of the furure spores,are to be seen in a more advanced stage of development,that is,in one nearer to multiplication.From this it follows that there is a stage of development during which the chromatin cannot be demonstrated;and also that another stage,- in which the chromatin globules,together with blocks of pigment,again become distinctly visible towards the periphery of the parasite,- follows this one.The chromatin is stained a different colour from the protoplasm in Romanowsky's method,and in it the process of nuclear division can be followed much better and uninterruptedly.Then the chromatin in every stage of development is clearly ro be distinguished from the protoplasm,it being of a purplish-red,while the latter is of a more or less deep blue.By this method,indeed, we find that some of the bodies with blocks of pigment,- usually the smallest,- are composed of a peripheral portion stained blue,- the protoplasm,- and of a central or sub-central part formed of granules or filaments stained red,- chromatin,- surrounded by a pale substance,- the nuclear juice,- which remains almost or altogether unstained.By the side of these are seen other bodies with blocks,- usually larger than the preceding,- in which are two or three clumps of chromatin,each one surrounded by a zone of a pale substance.These small masses,seen under a high power,appear to be dentate at the periphery,and to be composed of filaments so closely packed that in some specimens thay cannot be

clearly distinguished.In other specimens each of these collections of chromatin filaments is seen to divide into two distinct masses,which are at first very closely packed together,but later separate,and are then surrounded by a pallid zone,and arranged with more or less regularity in the protoplasm.Thus,by a successive series of divsions of the protoplasm,- at this point occurs the division of the body with the block of pigment into daughter bodies,- of the nucleus,we have the formation of a varying number of little round or ovoid bodies of chromatin which are readily stained and are compact in appearance,that is to say,without recognisable structure and apparently somogeneous.There is evidently a notable increase in the amount of the chromatin during the process of successive divisions of the chromatin.In each successive phase, the amount is greater;and,in comparison with that of the chromatin in the original solitary nucleus,that found in the a body with a block of pigment in which the daughter bodies are already formed is very great.Coming now to the multiplication,fission,or sporulation forms, the first thing that we have to note is that when the nuclear chromatin has,- as described in the preceding stage,- successively divided into a varying number of ovoid or rounded bodies, a portion of protoplasm arranges itself about each one,which then also divides;and thus fission is complete - a very small portion of protoplasm with melanin remaining non-utilised,and forming the residuum of segmentation.These forms which have undergone fission appear in fresh specimens like an accumulation or round or ovoid bodies gathered around a block of melanin,and occupying from a third to a half of the red blood-corpuscle in which they are situated;there are forms both smaller and larger than this.As in the spores of the quartan parasites,in each of the daughter bodies we see for the most part a small shining spot.The number and structure of the spores can be estimated exactly in stained preparations.Their number is somewhat variable;some small fission bodies with only six,eight,or ten spores take up not more than a quarter of the red corpuscle;other large ones,also endoglobular,have spores which form two rows around the block of pigment,and are as many as thirty or even more in number.In number the spores average from fourteen to sixteen.If we examine an individual spore,we see that it is composed of a little chromatin body,which is very strongly stained.It is called the nucleiform body,and is surrounded by a thin stratum of protoplasm. The form is round or ovoid.As a rule,there is a zone which is not visible.It is a pale zone,as in the spores of the tertian or the quartan,around the nucleolus;and it is to be found in only a few of the sporulating forms. The red corpuscle bursts open,and the liberated spores disperse in the plasma,when fission has occurred,perhaps as a result of swelling of the pale substance which is situated between the individual spores and constitutes a part of the residuum of segmentation.This exit of the spores can easily be seen under the miscroscope. The freed spores adhere to new red blood-corpuscles; and in grave cases we may see two,three,or more spores clinging to a corpuscle.These are easily distinguished

from young parasites by the fact that they have a determined and constant form which is round and ovoid;that they do not possess amoeboid movements; and that there is no vacuole present.Upon the formation of a vacuole the young amoeba assumes,in stained preparations, the typical annular appearance which differentiates it from the young bodies resulting from fission.The transformation of the so-called spore into a young amoeba occurs with the appearance of amoeboid movements and of the vacuole,which,it is to be assumed,plays an important part in the process of nutrition.It is probably as degenerative products,and not as spores,that the bodies resulting from the segmentation of an adult parasite must be regarded if they do not conform to the above description.In a fresh specimen we cannot with certainty recogbise an isolated spore,but must have recourse to appropriate staining.Spores in a fresh specimen can be recognised only when they are grouped in a characteristic manner. Not all parasites with pigment blocks give rise to multiplication forms such as have been described above.Another process,- which can be seen in every stage,and which is evidently of a degenerative nature,- is that some swell up,are feebly stained with aniline dyes,become vacuolated,and disintegrate into small, unequal,pale masses.It is now generally believed that about forty-eight hours are occupied,giving the tertian aestivo-autumnal fever,by the life cycle just described, from the non-pigmented forms to sporulation,with the invasion of new red blood-corpuscles.A study of the febrile curve shows that a rhythm in the fundamental febrile type is clearly to be recognised,just as a study of the life cycle demonstrates that the irregularities in its duration occur only within determined limits.It is believed that there is a variety of the same species,which completes its cycle in about twenty-four hours,giving a quotidian fever,but this point is still disputed by others.The duration of the human life cycle of this parasite is neither so regular nor so constant as that of the quartan,for instance, but has certain oscillations and irregularities;these are,however,not sufficient to justify the opinion of some authorities who refuse to recognise any law in the duration of the development of the parasite,or any type in the fevers producing it.The semilunar stage(of crescents,ovoid and fusiform bodies,round bodies of crescent origin,and flagellated bodies,regarding the origin of which,and the terminal phases,and the biological significance and the structure,there has been considerable disputation) represents the forms which begin in man the life cycle which is completed in the mosquito. The mere mention of the name is sufficient to indicate the shape of the crescents.They are cylindrical cells thinner at the two extremities than in the centre,transparent and colourless,a little longer than the diameter of the red cell,- from eight to ten micro-millimetres,- and in breadth one-third the same diameter,- two to three micro-millimetres,- curved in the form of a crescent;in the central portion are grains of needle-shaped rods of melanin.The two ends of the crescent appear to be united in the concave side by a very fine line.The outline of the parasitic body is indicated by a single very fine line; in some cases this may be double.The name also indicates

the shape of the fusiform bodies, which form is most frequently seen in grave infections and pernicious fevers. The size of the fusiform bodies is about that of the preceding forms, which they resemble in all their characteristics, except that they are not curved upon themselves. As a rule, their ends are very slender; the pigment may be gathered at the centre, and may be irregularly scattered in the parasitic body, or be arranged along the long axis of the spindle. The pigment is irregularly scattered, or more often collected in the central portion and arranged in the form of a wreath, in the case of the ovoid bodies. The latter also are shorter and thicker than the crescents. There is no amoeboid movement to be observed in connection with all these forms, and the pigment even is immotile. As a rule, however, when they are carefully examined under the microscope, we see some changes in their shape: thus, we may see a crescent become ovoid, and then become transformed into a round body, with a wreath of pigment also. It is long since since to became apparent to observers that all are endoglobular; and the very fine line which appears to unite the two curved ends of the crescents was regarded as the faint outline of the red blood-corpuscle. The corpuscle which contains them is always very pale; and sometimes, while the blood-cell is pale, the crescent form has a slight haemoglobin tint, as though it had attracted to it the colouring matter of the corpuscle, forming of it a sort of cuticle. Their endoglobular nature is now undisputed, though Laveran held that all the crescents were simply adherent to the globules, and that this adhesion was merely accidental. A crescent body appears to be formed of a vesicular nucleus in the centre of the parasite, around which are arranged needles or rods of pigment. There is no membrane; and we have also to note cytoplasm, which same surrounds the nucleus, and is more abundant in the portions corresponding to the greatest diameter of the fusiform body. Authorities have been at variance as to the presence of a membrane. Laveran, regarding the crescents as cystic bodies, thought there was a membrane; but this was disputed later, as a result of their microscopical observations, by Marchiafava and Celli, in the year 1887. Still later, in 1889, Celli and Guarnieri interpreted the double outline, which is seen in some but not in all of the crescents, as indicating the existence of a rather thick membrane. The same theory was held by Mannaberg, who regarded the crescents as syzygies resulting from the fusion of young parasites, and therefore provided with a membrane. It is true that the double outline is not seen at all, but only in a few crescents, but it remains when these change into spherical bodies. It is true also that this double outline is seen only in fresh specimens, and not in stained preparations; but Mannaberg rests his belief in the presence of a membrane chiefly upon the phenomena that occur during the process of flagellation. Nevertheless, the same phenomena may also be seen in the flagellation of the tertian bodies, that is to say, rapid undulatory movements of the contour of the parasitic body, and active movements of the pigment - phenomena which give the impression as of the existence of bodies moving rapidly within a cyst: and yet, according to the consensus of opinion, these have no membrane. A preconception resulting from the long persistence of these

bodies in the patient's blood, in spite of the administration of quinine, which appears to have no action upon them, is the theory that the crescents have a membrane; and it is the result, not of the direct observation, but in consequence of the preconceived notion that the crescents are resistant bodies. Antolisei would seem to have given the correct interpretation of the double outline seen in some of these bodies. He considers it to be a series of haemoglobin cuticle formed from the fed corpuscle, within which the crescent has developed. As to the round adult bodies of crescent origin, they have a sort of adventitious envelope, formed from the peripheral portion of the red cell which has gradually become more or less invaded by the parasite. The existence of these pseudocysts explains the impression, - the impression of a sudden liberation of the flagella from a restricted space in which they have been confined, - received by an observer of the change of a body of crescent origin into a flagellated body. In studying the structure of these bodies according to their method of methylene blue dissolved in ascitic fluid, Celli and Guarnieri noticed that at the centre of the crescent, and close to the clump of pigment was a small round body which was often stained blue, and which, according to these authorities, was similar to the little bodies which in the coccidia are regarded as nuclei. Later, Grassi and Feletti described in the crescents a vesicular nucleus which for the most part was round, situated in the middle of the crescent body, and provided (sometimes, however, it was not discernible even when the method described was employed) with a chromatin body, which these authorities called the nucleoliform node, which might be large or small, and which divided into two or four. By Mannaberg's method we frequently do not succeed in demonstrating the presence of chromatin in all crescent bodies; by the haematoxylin method of Bastianelli and Bignami, in the majority of instances, the so-called nucleolus cannot be seen - a fact which caused these observers to suppose that this formation was absent in bodies in the semilunar phase: especially as by the use of the same method they were always successful in finding the chromatin in the other phases of the aestivo-autumnal parasite. Since then, however, Ziemann believes that he has provided a morphological basis for the opinion that the crescents are sterile bodies; and this he claims to have effected by adopting Romanowsky's method, affirming that, as a rule, the crescents do not possess nuclear chromatin. Still, it is a fact that it was in consequence of the adoption of the very same method that Bignami and Bastianelli came ultimately to modify their early views upon the subject. They found that if preparations of blood were made in the usual way and kept in a moist chamber to prevent rapid drying, and then stained by the method in question, nuclear chromatin was very clearly seen in all the crescents, as well as in the ovoid and round bodies of crescent origin. The protoplasm was of a more or less intense blue colour, and the nuclear chromatin occurred in the form of violet-red granules. The granules of chromatin were hidden by those of melanin surrounding it in Ziemann's case; and this is probably why he, working with preparations which dried immediately, after mounting, did not observe the same. In preparations

kept in the moist chamber, however, as the nucleus and body of the crescent swell and the pigment needles disperse, the chromatin becomes invisible, swells somewhat, and is stained by Romanowsky's method in the typical way. It is apparently because the chromatin in the crescent bodies is much less readily stained in the latter, in the case of the young parasitic forms, that there is difficulty in demonstrating it by means of other methods, which, as we have already noted, give results that are not constant. For a considerable time past, the researches which have been carried out as to the origin and development of the crescents have shown that the bodies of the semilunar stage are developed from the aestivo-autumnal parasites, of which they represent a life phase that is constant. Even when they are less than a quarter of the size of the red blood-corpuscle, the young parasitic forms, from which the crescents originate, are distinguishable from the other forms of this species of parasites. They occur as small, round, ovoid, or spindle-shaped bodies, which, when seen in a fresh preparation, appear to be quite homogeneous, and to contain a greater amount of black pigment than do the bodies of equal size of the preceding cycle. The pigment, moreover, is in the form of little rods of somewhat large granules; and it is either irregularly disseminated in the body of the parasite, or collected chiefly towards the periphery. In their development these forms always tend to adapt their convex surface to the edge of the corpuscle itself; they are not motile; and they always occupy the lateral portion of the red blood-cell. Even the bodies which were originally round, with the progress of their development, tend to take on a long ovoid, or rather spindle, form, - so long as the distance between the poles of the ovoid or the spindle does not exceed the diameter of the red blood-corpuscle. It either keeps the same shape, or becomes curved and forms the true crescent, when the said distance is exceeded. There is a correspondence in the structure of the young forms with that of the adult bodies. One may observe, when stained by Romanowsky's method, a cytoplasm, which is coloured blue more deeply at the periphery than towards the centre, and a nucleus, which in the young forms is rather large in proportion to the amount of cytoplasm; the latter, however, during the further development increases in volume much more than does the nucleus. The nuclear chromatin is stained a purplish-red, and is usually in the form of threads or rods, sometimes of granules. In some cases, however, it collects at the centre of the parasite, and is surrounded by a pale zone; in other cases, again, the granules or threads of chromatin are disseminated more or less irregularly in the parasitic body, - but this latter appearance may possibly be due to some accidental variation in the preparation of the specimen. The young bodies, therefore, of the crescent stage are distinguished from the parasites of equal size belonging to the first, or pyrotogenous, cycle as regards the character and disposition of the chromatin. In the case of the peripheral blood, the various forms of development of the crescent body are rarely to be observed; for in it we usually find only the adult forms, the young forms occurring there only in grave infections with a large number of parasites in circulation, and not always then. The accumulation of

young crescents in the bone-marrow was noted, several years ago, by Bignami and Bastianelli; and the absolute exclusion of the possibility of this accumulation being an accidental circumstance has not been warranted by the results of autopsies in cases of grave infection. In the spleen we may find crescent bodies, and follow their endoglobular development, even when they are not found in the blood taken from the finger. It is in the case of pernicious fevers that a large number of young crescent bodies are to be found in the bone-marrow, and even when the same forms are very scarce in, or altogether absent from, the blood in other organs. These facts suggest that the bone-marrow is the chief, if not the exclusive, seat of the formation of the crescents. In spite of the above, however, Mannaberg believes that the origin of the crescent bodies may be explained on his theory that they are syzygies derived from the fusion of several young parasites; as to the mode of multiplication, however, he maintains some reserve, but holds that it is not impossible that there is a segmentation along the minor axis. His hypothesis is based upon what he believes to be an established fact, that the crescents possess a membrane, and upon the theory that the young forms, of which several were found within one red cell, end by merging into one body; the syzygy, according to his theory, is capable of multiplying later, and by its accumulation gives rise to the relapses. He, - in view of the fact that often several young parasites are to be seen in the same red blood-corpuscle, and sometimes as many as six or seven, appearing when very close together to be intimately adherent, - draws all the forms which might be considered as transitional between the young crescents and the flattened parasites, and fully describes them. His theory, however, has not been allowed to pass unquestions; for it has been urged against it that, in the first place, it cannot be held to have been conclusively demonstrated that the young parasites collected within one red corpuscle become merged together: on the contrary, they follow their own development, as shown by the fact that we often find several forms in process of multiplication within the same corpuscle, or various amoeboid forms in process of development. In the second place, the crescent forms, as we have seen above, do not possess a membrane of their own, but a species of adventitious membrane formed from the red corpuscle; and it is here to be noted that the formation of syzygium is usually followed by encystment. In the third place, there is direct evidence of the entire developmental series of the crescent bodies in the bone-marrow. The data furnished by recent investigations with regard to the development and the biological significance of these parasitic forms, as the same concern the later stages of the development of the supposed syzygies, do not sustain the theory of multiplication by segmentation. As first pointed out by Marchiafava and Celli, all authorities, in spite of the many and conflicting opinions expressed as to the origin and the significance of the crescents, agree that the latter proceed from the small amoeboid parasites, which multiply in the manner described by sporulation - parasites of aestivo-autumnal fever. That the crescents are derived from parasites which do not sporulate with the described succession of forms, - bodies with blocks of pigment, etc., - but form crescents only, is a theory advanced by Grassi and Feletti alone. They made of this a special genus,

the "Laverania", and to the species which occurs in man they gave the name, "Laverania malariae", in contradistinction to the parasites causing grave fevers, to which they gave the name "Haemamoeba praecox". From this it follows, therefore, that, according to these authorities, two species of two different genera are constituted by the various forms which we have described as comprising the two life cycles of the same parasite, that is to say, the pyretogenous and crescent cycle. After making systematic investigations in cases of aetival fever, by means of frequent punctures of the spleen, Bignami and Bastianelli gave forth their opposition to this view. They demonstrated that in all cases of this group, which are studied for a sufficiently long time without medical treatment, we can always follow the development of the parasites, on the one hand, up to the body with the central pigment and its fission, and on the other hand, up to the young endoglobular crescents. Apart from the fact that, by demonstrating the biological significance of the crescent bodies, more recent researches have absolutely excluded the theory once advocated by Grassi and Feletti, what we have just said proves that the crescents are merely one phase in the life history of the aestivo-autumnal parasite. It should not be forgotten that we often notice alterations in the crescent bodies, which must be held to be degenerative, and especially in preparations observed for some time. The process of vacuolisation of the ovoid, round, and crescent bodies can be plainly seen. For the most part, the parasitic body divides into numerous masses of unequal size, hyaline, and of simple outline, which gradually disappear within fifteen to twenty minutes, or a little more, as if they were dissolved in the serum. By watching this process of disintegration, we become sure that the crescents have no membrane, because, if there were one, it ought to become apparent during this procedure. Several writers have described a segmentation (= sporulation) of the similunar bodies (even those who acknowledge that they never have seen this up to the present time, hold that a process of multiplication must necessarily be present); and this, too, in addition to the above-mentioned degenerative alterations, which certainly constitute the final phase of the crescents, if they do not reach the surroundings adapted to their further development - viz., the mid-intestine of the mosquito. Two forms of segmentation of the crescents, - one of fission scarcely begun, the other of complete fission, similar to what is seen in the segmentation of the parasites of the regular fevers, - are claimed to have been seen by Grassi and Feletti. Mannaberg describes a transverse segmentation, which usually occurs in the middle of the parasitic body, dividing the crescent into two equal parts. Canalis describes the sporulation of round bodies of semilunar origin, and even gives a drawing of it. Golgi held that in the crescents there was a process of internal differentiation, which led to the formation and to the emission of young parasites which invade new red blood-corpuscles, whence occur renewed febrile attacks. It was upon the fact that the crescents persist in the blood during the apyretic interval separating, a group of febrile paroxysms from the relapse, that those who held

that there was a multiplication of the crescentic bodies,without being able to demonstrate it,based their belief;and they held that the same could be explained only by a process of sporulation of the crescents themselves.Those who have described and pictured this sporulation,- Canalis,for instance,described a sporulation in which the nucleus took no part at all,- were evidently led into error by their preconceived notion,and mistook a degenerative process of disintegration for sporulation. It is believed,however,that the crescents do not multiply in the human blood;for,as has been shown by Bignami and Bastianelli,the relapses of the fever are not in relation to the development of the crescent bodies,and, furthermore,even under the best conditions of research, one does not succeed in finding a fission form of crescents,which could with certainty be held to be a sporulation.The so-called flagellated bodies are the only developmental forms of the crescents which can be studied in preparations of blood.When such are exammined under the microscope,we find that some of the crescents are motionless,or only show change into ovoid or round bodies very slowly;others,however,so soon as they have become round in shape,exhibit lively movements of their pigmented granules,and suddenly shoot out filaments of their pigment granules,which same are endowed with great motility:in short,they turn into flagellated forms.It is supposed that flagellation is a phenomenon which does not occur so long as the parasite remains in the human blood;for the flagellated forms in question are never seen immediately after the specimens are prepared,but some time after the blood has been taken from the circulation.The filaments or flagella start from the periphery,either singly or at various pointsmor all together from one point,and sometimes forming a bundle which separates into two or three prolongations;and the so-called flagellated body is made up of a pigmented hyaline body,which is smaller than a red blood-corpuscle. The flagella are four or five times as long as the diameter of a red cell,sometimes longer,and are usually pointed at their free extremity,although they may be bulbous,or they may present swellings along their continuity.Their motion is continuous,or may be interrupted by pauses.Sometimes they meet and rub each other,as do the feet of a fly;sometimes they whip the neighbouring red blood-corpuscles,push them about rapidly and change their shape,then they become detached and move rapidly off in the plasma,scattering the red corpuscles which they meet.But sometimes their motion gradually stops before they become detached;and then,on careful observation,we find them after a while motionless and adherent to the pigmented body.During the movements of the filaments the pigmented granules of the parasitic body usually remain at the centre;but they may be carried to the periphery,and even penetrate into the prolongations,- which then appear to be canalised,- where they exhibit rapid movements - either in the direction of the free ends or backwards into the pigmented body again.The movements of the pigmented granules within the pigmented body sometimes cease during the motion of the filaments; but,again,they may continue for hours,even after the filaments have stopped moving and have become detached.

It is extremely rare in a fresh specimen to see a flagellated body in which the including red blood-corpuscle is distinguishable, that is to say, a round body in which there are flagella which can be seen to be endoglobular; but the fact that the flagellated body is within a completely decolourised corpuscle is, in the case of a properly stained preparation, from the observation of, around the parasite, the shadowy outline of the red cell in question. The movements cease, and all traces of the prolongations are lost, while the pigmented corpuscle remains distinctly visible, when we add a drop of distilled water to a specimen under the microscope in which there are bodies with flagella in active motion. Nevertheless, the form and the movements of the flagella are not in the least affected by a physiological solution of sodium chloride. There are also other points to be noted in this connection; for, in addition to the above, one may observe the emission of small, round, hyaline bodies which have become detached from the edges of many of the various forms of the crescent stage, that is to say, as well from the crescents as from the round or flagellated bodies. This process has by some been described as that of germation; and in it the little bodies become projected at the edges, and then detach themselves, and either move away from the parent body or remain close to it. From one body of the crescent stage as many as two, three, or even five little bodies may thus make their exit. The emission of flagella, however, is not the end of all the actively motile bodies of the crescent stage; for there have been described, by Marchiafava and Celli, special bodies with an undulatory movement of the contour. These bodies may be seen to revolve in one direction and then in another, while their peripheral portion is the seat of the most rapid undulatory motions; at the centre they have a pigmented nucleus which is either motionless, or seems to swing in correspondence with the peripheral oscillations. The movement of these bodies lasts from twenty to forty minutes, when it slackens, becomes intermittent, and finally stops. It is necessary to examine preparations stained according to Romanowsky's method to acquire an exact idea of the structure of these bodies, and of the flagella especially, though all this may be seen in the ordinary fresh specimens. The flagellata of a haematozoon, found in the blood of young crows taken from their nest in malarial regions, were studied in this way by Sakharoff. He calls the same a phenomenon of degeneration, and describes the so-called flagella as chromosomes which have come out of the nucleus of the parasitic body, and flagellation as a process of perverted karyokinesis. Using preparations in which the blood was spread in the usual manner on the cover-glass, and which was kept in a moist chamber for ten or twenty minutes or more, and then rapidly dried in absolute alcohol for twenty-five or thirty minutes, Bignami and Bastianelli have more recently made use of the same method in the study of the structure of the flagellated bodies derived from the crescents. Under these circumstances, many of the crescents become flagellated (those that do not usually undergo changes presently to be described); indeed, Marshall, Ross, and

Manson have demonstrated that a certain amount of moisture and of exposure to the air favour this phenomenon. There is usually a certain amount of swelling to be seen in these preparations of the crescentic and round bodies; even the nuclear chromatin swells and takes on the form of granules, or blocks, or filaments. The so-called bud is seen occasionally, that is to say, when some minute chromatin masses make their exit from the parasitic body and adhere to the periphery of the latter. We usually find four for each body, rarely more, in stained specimens in which the number of flagella can be accurately observed. The flagellata themselves are made up of a pigmented body, which takes on a blue stain, and in which the chromatin is divided into blocks arranged along the periphery; from these the peripheral chromosomes project filaments which, surrounded by a very thin layer of protoplasm, constitute the individual flagella. In cases in which we see an isolated motile filament or flagellum, one which is completely formed, we find that the chromatin tends to be massed at the centre, the extremities being formed of protoplasm; the chromatin may also occur in the form of a series of granules or rods instead of filaments. The morphological characteristics above-mentioned are not, however, possessed by all the flagellata; for there are some in which the filaments do not contain any chromatin, but are composed of protoplasm alone, and others in which there may be one or two filaments provided with chromatin, the others beinf formed of protoplasm. Such forms are to be considered as incomplete: that is to say, as flagellata whose development has been interrupted by desiccation. In fact, it is in the place where it naturally occurs, that is to say, in the mid-intestine of the Anopheles, that these forms, as well as some others or irregular aspect are to be found, being never seen in the moist chamber or at all when the process of flagellation is completed. Characteristics, differing somewhat from those of the bodies which give origin to filaments, are exhibited by crescents which do not become flagellated when kept in the moist chamber under the same conditions as the others. They swell, and their cytoplasm takes on a deeper blue stain, the chromatin is in smaller amount, and is gathered in granules and rods in the nucleus, which is either central or subcentral or surrounded by a wreath of pigment; but, as a rule, a certain number of granules of chromatin, - which constitute the so-called buds, which may be found at the periphery of the flagellated bodies and can be seen in fresh preparations, - are to be seen to have made their exit from the nucleus, and to be adherent to the periphery of the cytoplasm. Those which become flagellated, and others which do not and which differ from the first in some minor morphological details, are the two classes of crescent bodies which we must therefore recognise. It may here be noted that very many different theories have been advanced as to the biological significance of the crescents, as well as that of the bodies derived from them. Some of these we can dismiss at once, taking note only of the facts demonstrated regarding structure. It is easy to do away with the idea that they are bodies capable of multiplying in the human blood, as was held by some who reasoned by analogy rather than

from established facts,and also by Golgi,Antolisei, Canalis,and Grassi and Feletti.In like manner it is contrary to reason to admit that they are cystic bodies,as Laveran and Mannaberg believed,since it has now been proved that they have no membrane.Nor is it to be admitted that they are resistant spores,as was believed by Councilman,who was struck by the resistance opposed by these forms to quinine,and this because of what has been learned in regard to their biological properties,and because of the facts already described in relation to their ultimate development.The hypothesis that crescents are sterile bodies is the one usually opposed to these views.Bigmami considered the crescents to be forms of divergent and interrupted development of the aestivo-autumnal parasite;he said forms of divergent development because,following the life phase of the parasites,he thought he observed that,at a certain point in their growth,while some were preparing to multiply others deviated from their course,and,without multiplying continued to increase in size until they formed typical crescents;he added forms of interrupted development because,at a given moment,these forms, without multiplying,degenerated in various ways and disappeared in the blood.The same theory was taken up later by Bignami and Bastianelli,who undertook the ystematic study of peripheral and of splenic blood from patients suffering from primary aestivo-autumnal fevers,with the view of ascertaining the time in the course of the disease at which the first crescents appeared,how long they perisited in the blood,what was their relation to relapses,etc.Furthermore,it was ascertained by these researches that no crescents were ever seen to multiply,and that they could not be held to be the cause of relapses:these writers held that they were the sterile forms of the aestivo-autumnal parasite. In 1894,they endeavoured to explain the sterility of these bodies by the thoery that the crescents have the same biological significance as the forms belonging to several other parasites which complete their life cycle outside the organism in which they are found. They affirmed that it is a well-known fact that two cycles of development have been demonstrated in several endocellular parasites belonging to the group of the coccidia;One cycle of development is completed exclusively during the parasitic life;but after the parasite has lived as such during a series of generations,there berins a second life cycle,represented by forms which can terminate their development only in the surrounding atmosphere or in the tissues of some other animal; Should these forms of the second cycle not make their exit from the body of the animal in which they started, they remain sterile,and after a while degenerate and die.These writers,then,believed that the crescents were sterile forms in man and for man;and this view is the exact statement of a fact which has now been established, if the observation be limited to what occurs in human blood,as was the case until comparatively recently. A full solution of the biological significance of these forms has been arrived at;for the fact that the crescents reached the tissues of another animal,- i.e.,the mid-intestine of the mosquito,- and there complete their life cycle,has been shown by the most modern researches.Various theories have been advanced as to

the significance of the so-called flagellata.The final and perfected phase of the malarial parasite was what Laveran considered his motile filaments to be;but these same structures were looked upon by Marchiafava and Celli as protoplasmic prolongations of the pigmented bodies,having the significance of flagella;and they regarded the flagellated bodies as representing a later development of the pigmented plasmodia.On the other hand, Grassi and Feletti held that the so-called flagellata were merely a product of the degeneration and destruction of the adult parasites.These theories have,of course,been been demolished by modern researches regarding the structure of these bodies;as has also the opinion of Labbé who likewise considers them to be forms of death, not found in the living organism,but outside of it only, a product of the physiochemical action which modifies the plasma and the corpuscles which are withdrawn from the blood-vessels.The opinion that the flagellated bodies represent the first principle of an extra-human phase of life,which dies from lack of a suitable soil, has been expressed by Mannaberg:who also affirms that, if these were forms of death,there would be no explanation of the fact that they are seen only in a limited number of parasites.The theory that the flagella are pre-formed within the crescents and the round body,from which they make their exit when both crescents and round bodies are outside the human organism,has been advanced by Manson.He has also endeavoured to demonstrate, by staining with carbolised fuchsin,the presence of the filaments pre-formed within a delicate cyst.According to this theory,the flagellum is a special form of spore, which is developed only in the outer air,"in the interest of the extracorporeal life of the parasite"- the seat of this ulterior development the body of a suctorial insect,specifically the mosquito.This theory,however, has not been sustained by later researches.In fact,a study of the structure has shown that the flagella are not pre-formed in the crescents and the round bodies; within these we find the filaments of chromatin which go to make part of the flagella,but not to form them in their entirety.That the pigmented bodies,and not the non-pigmented flagella,are developed in the mosquito has,finally,been demonstrated by the researches of Ross,upon the proteosoma of birds,as well as by those carried on in Rome upon the malarial parasite in man. There seems now every reason to believe that the crescents and the flagellata are sexual forms of the malarial parasite,and that a new being,which begins its existence in the tissues of the mosquito,is produced by a reproductive act,in which the flagellum represents the male element and an adult crescent the female cell. This theory has been founded,in the first place,upon the sexual phenomena which occur in various sporozoa. Simond was the first to propound the theory that the flagellata of malaria are sexual forms.He studied the life phases of coccidium oviforme,of cariophagus salamandrae,etc.,and found in these parasites two cycles: First,a cycle which he called asporulate,which is completed in the host,and gives rise to the formation

of falciform corpuscles, merozoites; and, second, a sporulate cycle, represented by the encysted forms, which is completed outside the host, insuring the life of the coccidium in its new surroundings. Now, this second cycle begins by an act of fecundation, the male element being represented by an adult form in which the nuclear chromatin is divided into a large number of filaments which separate and go to the periphery of the parasitic body, from which they emerge and remain for a while adherent to its edges like a horse's mane and then detach themselves, being surrounded by a thin layer of protoplasm. In fresh specimens this process occurs with so great rapidity in movement that the bodies appear to be flagellated. The filaments are spermatozoa which fecundate the young coccidia, and these then begin the sporulation cycle, or the cycle by which is assured the conservation of the species outside the host, and the possibility of fresh infections. Our author, these facts being established, expresses it as his opinion that the polymitus of Danilewsky and the flagellata of malaria have the same functions as the pseudo-flagellata of the coccidia, as well as the same significance as the latter. During the time that they were investigating the development of the Adelea ovata and the Eimeria Schneiderei, Schaudinn and Siedlecki were able to follow, in the most complete manner, the development of the sexual forms and fecundation; they describe the accompanying nuclear modifications (the latter observer later, - in 1898, - studied similar phenomena in another coccidium). Applying zoological nomenclature to the coccidia, they call the sexual forms, in general, gametes, the female elements macrogametes, the cells producing the male element microgametocytes, and the male elements microgametes. MacCallum tried to discover whether sexual forms and phenomena of copulation were to be found in some haematozoa, and succeeded in witnessing, under the microscope, the act of fecundation in the Halteridium of birds. He divides the adult forms of the Halteridium into granular forms and forms of a homogeneous hyaline aspect, the latter only becoming flagellated. A flagellum penetrates into a granular adult form, which, after fecundation, becomes changed into a motile body resembling the so-called vermiculus of Danilewsky. The penetration of a flagellum, into a round body of crescent origin with wreath-shaped, was twice seen by him whilst studying a case of aestivo-autumnal fever in man, in which there were many crescent forms. Indeed, the theory of fecundation must be considered as the most consonant with the latest knowledge in regard to the biology of the sporozoa; in the latter it would seem that the sexual phenomena are constant, and that the formation of the encysted forms, which begin the cycle that is continued outside of the body, is preceded by the sexual act. That the forms which pass from man to the mosquito are sexual forms, and also that an act of fecundation initiates the new life cycle in the middle intestine of the insect, may therefore, and reasoning from analogy, be taken as in the highest degree probable. In support of this theory may be the comparatively recent researches of Bastianelli and Bignami, according to which, by the use of Romanowsky's staining process, we find two kinds of crescentic bodies, differing in the amount of their chromatin, which is greater in the forms which become flagellated, and in the staining of the cytoplasm, which in the non-flagellated forms is of

a much deeper shade of blue.The female elements,or the bodies which do not become flagellated,are usually now called the macrogametes;the crescent bodies are termed the gametes;those which become flagellated,or the male elements,are known as the microgametocytes; and the individual flagella are designated the microgametes - after Svhaudinn and Siedlecki,who have studied the sexual forms of the sporozoa.The new life cycle, which is completed within the tissues of the mosquito, begins with these phenomena,whose seat is naturally not the outer world,- where they were at first chiefly observed,- but the middle intestine of some species of the insect in question.The fact that all these parasitic forms consist of a nuclear formation,whose constituent parts are not seen with equal clearness in all the various stages of their existence,and of cytoplasm, would appear from the above description.It is important to remember this at the very outset of the study of the general morphological and biological properties of the aestivo-autumnal parasites.Regarding the nuclear formation,all that we see in the very young forms is the chromatin globule;and to this various writers have given different names.Mannaberg and others call it the nucleolus,Grassi and Feletti the nucleoliform node, whilst most authorities prefer,as a rule,to designate it as the small body of chromatin - in order to avoid cytological discussion.Similar bodies have been described in many lower organisms - as,for instance,in the coccidia;some writers,following Labbé,call them karyosomata,others,such as Rhumbler,call them Binnenkörper (which same,in view of more recent researches,apparently are not the same as the nucleoli of the cells of the higher organisms) - in order to adopt an indifferent name.In some coccidia these small inner bodies,or Binnenkörper,can be distinguished from the nuclear chromatin,which is arranged in threads and granules;and we can see what becomes of each during the process of division, as Schaudinn and Siedlecki did in the case of Adelea ovata.A clear distinction between the nucleolus and the nuclear chromatin is not,in the case of the aestivo-autumnal parasite,permitted by the various technical methods at our disposal.A light zone,which is supposed to be nuclear juice and which is not apparent in the forms that are very young,is seen in bodies,which are in the course of development,around this chromatin body.Many writers affirm that the nuclear membrane circumscribes the clear zone.It can,however,only be demonstrated in the adult bodies of the second cycle - i.e.,in the crescents.We can only assume the probability of its presence - first,by the distinctness with which the nuclear formation is seen to be separated from the cytoplasm;and,secondly,by analogy with what is known as to similar organisms,whose structure,because of their greater size,can be more easily studies: for,by none of the methods in use,can we find it with any certainty in the young and in the developing forms,and even less in those undergoing multiplication.The contents of the cell,the protoplasm or cytoplasm,as already mentioned, becomes pigmented at the periphery;but,in the case of the crescents,we find the pigment gathered in the innermost portion of the cytoplasm,immediately surrounding

the nuclear formation.It has been described as a vacuole, which is almost constant in the very young forms,and which disappears in the course of their development. That its presence is the cause of the annular forms assumed by the plasmodia in fresh preparations,and of the appearance which these same take on in preparations stained according to Romanowsky's method (in which they are seen as thin blue lines,in which,while the central portion,or vacuole,is pale or colourless,the chromatin body is seen of a purplish-red colour),is the opinion held by the majority of observers.We have also noted the fact that,in the case of the young forms,the phenomena of motion is very lively,and that this same diminishes by degrees,to cease entirely during the stage of multiplication.These movements cobcern the protoplasm; but it is probable that the nucleus also has amoeboid movements.Except such as accompany the formation and extrusion of the motile filaments,in the crescent cycle we have no movements.It is by the successive division of the nuclear chromatin,- rudimentary forms of karyokinesis,- within an adventitious cyst formed by the red blood-corpuscle,that multiplication occurs.These little bodies resulting from the division are not provided with a membrane;they have been called spores or gymnospores,and the process of their formation sporulation, because these expressions are in current use amongst naturalists to indicate multiplication by segmentation in similar organisms.It is to be remembered,however,that the meaning is not the same at all as that of a spore in bacteriology.In fact,these spores of the malarial parasite have none of the biological properties of the enduring spores of bacteria,that is to say,they are not endowed with special powers of resistance;and,as regards their structure,as has been said,they do not differ in any essential points from the young plasmodia.Bastianelli and Bignami have suggested that some spores which were born naked might,under special conditions,acquire a membrane and lose their capacity for staining;but this is a theory put forth in explanation of cases - a few - in which,during a period of latent infection,it has not been possible to find,even in the spleen,any parasites to the presence of which could be referred the occurrence of a late relapse.Furthermore,proof of this theory has not yet been forthcoming.Antolisei held that the spores of malarial parasites were provided with a membrane,- clamidospores,- but this view has not been confirmed by more recent researches.The red blood-corpuscles are the seat of the development of the aestivo-autumnal parasites,just as they are of the others. Laveran thought that the parasites were free in the blood;but,later on,Marchiafava and Celli,- who also noted that,in certain cases,the plasmodia were only partially enclosed in the red blood-corpuscles,as though they were about to leave them,- held that the plasmodia were endoglobular - this view being based upon the fact that their pseudopodia never went beyond the boundary of the red cell.Furthermore,the amoeboid bodies are seen as if floating in the protoplasm of the corpuscles, becoming less visible,or,as it were,submerged,and then reappearing,one or two prolongations first becoming

visible, and then the entire body. Although he still believed in the position of the adult bodies being endoglobular, Mannaberg ultimately expressed his doubt as to whether the young plasmodia - the non-pigmented plasmodia of Marchiafava and Celli - were within the red blood-corpuscle. He says that a direct proof that some forms are endoglobular is found in the observation of the spherical bodies of the crescent stage, or the large tertian bodies, at the moment when they are leaving the red corpuscle, for it is possible to doubt that they make their exit by the bursting open of the corpuscle itself. But the small non-pigmented forms, according to him, long remain simply adherent to the globules. He says that it is very difficult to determine whether a parasite is within a corpuscle, or simply adherent to it, or, as it were, pressed into its surface: in the latter case it might be that the pseudopodia were unable to go beyond the limits of the corpuscle, - as noted by Marchiafava and Celli, - simply by the fact of their viscidity, which might prevent them from becoming detached from the cell. He affirms that there is a sort of depression in the corpuscle which contains them. Such depression, with distinct edges, on the surface of the corpuscle, according to him, can be seen by means of oblique illumination and an open diaphragm, allowing of the examination of the body in relief. The endoglobular nature of the vast majority of the parasites, even the young non-pigmented forms, however, is believed in, nonetheless, in spite of all this. Especially is it worth noting that, if we once admit the endoglobular situation of the developing and the adult forms, the question loses all its interest, and there remains simply for us to ascertain at what period of their development the young parasites enter into the substance of the red blood-corpuscle. It is now generally held that the theory that the majority of the young forms are endoglobular is demonstrated by the fact, which has already been considered, that, by following their motions, we can see them apparently becoming submerged in the substance of the corpuscle, and then emerge from it again. Furthermore, in the cadaver, in which the parasites have lost their amoeboid qualities, we sometimes see them moving in toto, with a floating motion, within the corpuscle, as though the contents of the red blood-cell were liquefying. That the globule is tranformed into a little bladder full of fluid, in which the parasite is seen to oscillate if the corpuscle is moved, is the impression received. We have already dwelt upon the fact that the young parasites sometimes seem yo be imbedded or pressed into the surface of the corpuscle; but forms, which are at the beginning of pigmented stage, are scarcely ever seen in this position but are always endoglobular. From this it is evident that, after remaining for a short time adherent to the red corpuscle, the young plasmodia penetrate within its sustance; and this occurrence is essential to their further development. Though the latter is in site endoglobular, that there is an equal distribution of parasites throughout the vacular system does not follow therefrom. The mechanical conditions of the circulation differ in the various viscera, and, moreover, as each viscus modifies in a special manner the blood

which circulates in it, the conditions of development for the parasite must differ in the various organs. It is an interesting fact that the parasites in their several life phases, while still endoglobular, may have a predilection for certain situations. Thus, the young forms of the pyretogenous cycle circulate in the blood, while the adult forms, bodies undergoing multiplication, and fission forms, as a rule, remain stationary in the internal viscera. This may be partly due to the alterations produced in the corpuscle as the parasite develops, but it is partly, and chiefly, owing to a special biological property of the aestivo-autumnal parasite. The bodies of the crescent group behave differently, the young ones being found only within the vessels of the viscera, and are chiefly, if not exclusively, formed in the bone-marrow, while the adult forms enter the general circulation. The adult crescents are the bodies which, when taken in with the blood by the mosquito, continue their development in the intestine of this insect, and, therefore, they have just so much more chance of completing their life cycle if they circulate in the blood for several days. In short, we must see in these facts a phenomenon of adaptation. Before leaving this subject we must consider for a while the parasites which complete their entire life cycle without becoming pigmented. The theory that this represented the multiplication of these plasmodia was, in 1885, suggested by Marchiafava and Celli. They described small endoglobular fission forms that did not show the smallest trace of pigment; and drew attention to the fact that the fission in question of the plasmodia may occur even before the red blood-corpuscles in which they have developed are entirely destroyed. They stained sections of the cerebral cortex with vesuvin, in some cases of pernicious fever, and found that the capillaries were overfilled with red corpuscles, many of which contained parasites in all stages of development, all of which were non-pigmented; these were forms already divided into small clumps of ovoid bodies all of equal size (staining like the so-called spores of the malarial parasite, and sometimes arranged in rosette form), young discoid forms, and forms in process of division. These authors concluded from this that there are malarial parasites which may complete their whole cycle of development without becoming pigmented, and believed that there may be an absence of melanaemia in certain cases of malaria. Bignami (who studied the parasites in a large number of cases of pernicious fever), Marchoux (who studied the malaria of Senegal), and Smith and Kilborne (who found in the Texas fever of cattle, - as did also Dionisi in bats, etc., - endoglobular parasites which completed their whole life cycle without producing pigment), as well as others, have confirmed these data. As far as permicious fevers, at least, are concerned, it must not be forgotten that for these researches we can make use only of fresh specimens, or of those which have been preserved in alcohol for a short time only. We know, in fact, that the pigment may gradually disappear altogether from the brains kept for a long time in alcohol; so that, when we find in them non-pigmented fission forms, we cannot be sure that the loss of pigment is not artificial.

Furthermore, until the complete absence of melanin has been demonstrated by repeated punctures of the spleen, we can never be certain of the existence of an infection without melanaemia. It is only in the absence of black pigment that the forms in process of development differ from the ordinary aestivo-autumnal parasites; and, for the most part, rarely more than eight to ten spores are to be seen in the fission forms without pigment. The question has been raised as to whether these forms represent a definite parasitic species, or whether they are aestivo-autumnal parasites, which before the pigment has formed have undergone a process of premature multiplication. Some writers support the first opinion; thus, Mannaberg speaks of a quotidian due to a parasite which does not produce pigment. Until further discoveries are forthcoming it is, however, inadvisable to dogmatise on this point; for, in cases in which some have found non-pigmented fission forms, there have always been pigmented parasites as well. It is also noteworthy that the usual fission forms have been found in the spleen with blocks of pigment, though in the vessels of such an organ as the brain, all the parasites in every stage of development might be non-pigmented - the complete life cycle being under observation. A pure culture of the non-pigmented parasites has not, so far as I am aware, been up to the present time forthcoming, that is to say, we have no example of a well-studied cases in man, in which all the parasites in in the vessels of all the viscera are without pigment. However, in view of the fact that they have been found only in tropical or in pernicious fevers, and that they are always found in company with parasitic forms that could ~~not~~ be diagnosed with absolute certainty as aestivo-autumnal, it is belived that these forms may be considered as realated to the organisms of the summer-autumn fever.

Life Cycle of the Malarial Parasite in the Mosquito.

The behaviour of the malarial parasite in mosquitos has attracted considerable attention; and much has been published from time to time regarding the procedures of research instituted. Some experimenters have tried to gain information on the conduct of the parasite outside the body of man by starting from the known forms in that personage; whereas other have sought for them directly in the air, the dew, or the water of marshes. The object of the first was to cultivate the human parasites in various culture media, modifying in various ways the ordinary media used in the study of bacteria. This was the procedure of Marchiafava and Celli in their earliest experiments. The secomd class of investigators searched in the atmosphere, and in marsh water, for free living organisms resembling the parasite in man: this was done by Laveran, who speaks of finding motile filaments in water, similar to those in malarial blood. Others, as Silvestrini, injected the washings from malarial earth (and Celli and Sanfelice did similarly in the case of birds), marsh water, etc., under the skin, in order to ascertain whether they could in this manner produce a malarial disease. Grassi and Calandruccio

for a while thought that they had found the malarial parasite existing freely in the earth.But the failure of all these experiments caused several investigators to think that their researches must be turned in other directions in order to solve the problem,and that possibly the plasmodia were to be found as parasites in other animals,and not in the free state outside the body of man.The intimate relation between malarial and certain insects is,indeed,a popular belief in several malarial districts.Now,since the theory has been proved to be a fact,various authors have endeavoured to find in the earlier writers the first allusion to this allegation.At the beginning of the eighteenth century, Lancisi,who actively upheld the theory of a close relation between malarial fevers and marshes,attributed to the effluvia of the latter their injurious effects upon man.He appears to have attached importance to everything which,originating from stagnant waters,can in any way attack man,including mosquitos,- to which he pays particular attention,noting their abundance in marshy regions,and above all the abundance of the "vermiculi",whose transformation he noticed"in stridulos culices",- and other insects.He assumes that there may be several ways in which these insects may have an injurious influence upon the inhabitants of malarious localities.He expresses the suspicion that the injurious action may be due to the ingestion of waters rendered foul by the insects;but,what is of more interest,he also admits that they may do more harm by their stings - not simply by stinging,but by the injection of a toxic substance in the act of puncturing the skin.He adds that the insects - the"animated effluvia"of marshes - may vitiate our systems not only by the effects of the local irritation,but by the liquid which they leave behind after their sting.Besides this writer,others since his time have maintained a cautious attitude on the question,admitting that the vehicles of infection might be many,and that the parasites may be found in both the earth and water of marshy localities,and might be communicated to man through the ingestion of infected water.This was the attitude of Laveran,who,in contradistinction to Lancisi in the previous century, did not even hint at the possibility of inoculation, but who,with him,held that man can be infected in various ways.He searched for the parasites in water, which he considered to be the chief,if not the only, vehicle of infection;and as to the mosquitos,he propounded the theory that they may take the parasite from man and then infect water,as they do in the case of the filaria.Since,taking into consideration the condition of knowledge at the time of its inception and when demonstrative facts are sought,no hypothesis can properly be called scientific unless it is sustained by a sufficient number of arguments to give it some probability,it is only within the most recent years that the mosquito theory can be said to have really entered the re alm of scientific discussion. There are at the present time two ways in which investigations are pursued - those of Bignami and Manson.It was the first-mentioned observer who,endeavouring to ascertain how fevers are taken,showed how great are the

difficulties met with in considering the air and water as vehicles,and demonstrated the probability of inoculation by the mosquito,dwelling upon the analogy of human malaria with Texas fever:furthermore,since 1894 he has endeavoured to prove these views by experimental demonstration.The other method has been followed by Manson,who,taking up Laveran's theory,tried to find out what were the forms of human parasites which were capable of passing into mosquitos and there continuing their development.He considered the flagella to be spores,which becoming free in the mosquito's intestine from the cysts containing them,continued to develop, and at the death of the mosquito became free in the water,which thus was converted into a vehicle of infection to man.These two theories seemed at first to be so absolutely contradictory that they gave rise to written discussions,which have certainly been of use in stimulating the study of the subject.Especial subjects of discussion were the significance attributed by Manson to the flagella,which is not upheld by fact, and the importance attributed to the Laveran-Manson theory of water as a vehicle of infection,which is contradicted by accurate epidemiological observations, as well as by actual experiment.By demonstrating the fact that mosquitos take the parasite from man and inoculate man with it again,further research has led to a harmony in fundamental opinions.Manson's theory had the great merit is serving as a guide to the researches of Ross,who,by causing birds infected with proteosoma (Labbé) to be stung by a species of mosquito (gray mosquito),determined in the latter the forms of a new parasitic life cycle.These were found in the walls of the middle intestine where,according to Ross,the proteosoma assumes the aspect of a coccidium (proteosoma coccidia);in the mature capsules of these coccidia were formed germinal corpuscles (germinal rods),which accumulated in the poison-salivary glands of the gray mosquito,healthy sparrows being capable of becoming infected with the proteosoma at this point.The important fact that not every species of mosquito can give lodgment to a given haematozoon (in fact,Ross found the developmental stages of his proteosoma coccidia only in the gray mosquito) has been forthcoming from these researches,which gave us our first information upon the life forms of a haemosporidium in the body of a mosquito. That only a determined species of mosquito can transport the infection to man was rendered more probable than ever by the same;whence the necessity of a preliminary zoological study upon mosquitos of malarial regions,with the view of ascertaining the dominant species.With this idea Grassi,investigating the distribution of mosquitos in malarial regions,in the summer of 1898,came to the conclusion that in malarial countries, in addition to the species found in non-malarial regions,there are others which are completely absent from the latter places.In malarialregions we find in large number the Anopheles claviger,other species of Anopheles,the Culex penicellaris,and other species of Culex which must be naturally be open to suspicion if the mosquito theory of the origin of human malaria be once admitted.In non-malarial countries the Culex pipiens and other species of Culex predominate.These points were now fully investigated.With these species

Bignami obtained in Rome the first case of experimental malaria in man, this being reported in 1898 (November). In rapid succession there followed the observations of Bignami and Bastianelli,- upon the development of human parasites in mosquitos of the genus Anopheles, and especially in Anopheles claviger, which was the chief one to attract the attention of these observers, because of its abundance in the Roman Campagna,- and of Grassi. These observers have shown that the parasites of human malaria pursue in the Anopheles a life cycle resembling that described by Ross in the case of the proteosoma in birds.

From the foregoimg remarks it will be evident that the malarial parasite of amn can be entertained by only certain determined species of mosquito. It is necessary, then, to describe this class of insect, that is to say, the genus Anopheles Palpi are present in both sexes, about as long as the proboscis. The palpi in the female are four-jointed, but in the basal joint there is a constriction towards the root, which apparently forms a basal articulation, and gives the palpus the appearance of being five-jointed; another constriction sometimes makes it seem six-jointed. The palpi of the male are really three-jointed, but appear four-jointed by reason of a constriction in the basal portion towards the root; and sometimes the presence of two constrictions, one towards the middle of the long portion and one in the apparent basal joint, gives the appearance of five or six articulations. The appearance of five joints in the female and four in the male is the usual one. In the female the palpi resemble straight filaments, which in repose are parallel with the proboscis, forming with it a bundle of three parts; when the female stings, they rise and diverge; in the female the antepenultimate joint is as long as, or longer than, both the penultimate and ultimate. In the male the palpi of the last two joints are short, thick, and olive-shaped. The mucha has a posterior crown of scales. The legs are very long, ending in simple or dentated claws or in ungues. The abdomen is pilose on both its dorsal and ventral surfaces, but there are no squamae, which are abundant in the genus Culex. Five species of Anopheles are to be found in Europe, which, according as to whether or not the wings are spotted, are divided into two groups: Those without spots but possessed of wings include the Anopheles bifurcatus, the Anopheles villosus, and the Anopheles nigripes. The Anopheles bifurcatus have wings without spots. The species is less black than the following, and of medium size. It is much less abundant than the Anopheles claviger in the Roman Campagna. Some individuals may be smaller and brownish-black, some larger and brownish-yellow. The Anopheles villosus resembles the bifurcatus (Ficalbi thinks that possibly it may simply a variety of this and not a species at all), but is larger and more pilose. Ficalbi thinks that the Anopheles nigripes, instead of constituting a distinct species, may be a small and dark specimen of bifurcatus which he has had frequent opportunities of observing. It has wings without spots, like the preceding; also a proboscis, palpi, tibiae, and tarsi blacker than in the Anopheles bifurcatus; and it is not more than 8 mm.,

that is to say,it is smaller in size.He says that it belongs to Northern Europe,and is rare.In the category of spotted wings we have the Anopheles claviger and the Anopheles pictus.The former is also termed the Anopheles maculipennis,and has wings with four spots formed by masses of chitinous squamae.Femora of the anterior pair are not enlarged at the base.With the exception that the Anopheles claviger has the spotted wings and is in appearance somewhat more yellowish,the description of the Anopheles claviger agrees with that of the Anopheles bifurcatus.The wings are brown,especially in the female,or slightly yellowish-brown;and the total length of the body,including the proboscis,of the female is 7.5 to 9 mm.,the female being always larger than the male.Even with the naked eye,we can distinctly see the four black spots,which are,as a rule,more conspicuous and better developed in the female than in the male,and are so placed that,if joined by an imaginary line,they would form a capital L.Under the magnifying glass we see that the wings are rich in black scales,an accumulation of which produces the spots.It is in well-watered plains that this species is so abundant; and it appears to be disseminated throughout Europe, being found in England,Scandanavia,Austria,Germany, Russia,etc.It is largely disseminated in Italy,where it is the most common species of the genus Anopheles,and is commonly called the zanzarone ot big mosquito. Regarding the Anopheles pictus,we may note that the wings,even to the naked eye,seem to have blackish-brown and rather tawny lightish-yellow spots,due to the accumulation of squamae of these colours.In the proximal third the femora of the anterior pair are slightly enlarged.The anterior margins of the wings,as far as their tips,are of a blackish-brown colour,which is interrupted by three yellowish marginal spots.The central coloured spot is the largest,the posterior the smallest,the latter not touching the margin of the wing.Five or six brownish spots,sometimes seven,are produced,in the remaining portion of the wings,by the of the black squamae of nervation accumulating at certain points,and alternating with yellow squamae.There are black scales on the posterior margin of the wings; and these,at a point corresponding to the anterior third of the margin,are of a tawny lightish-yellow colour,forming marginal spots of that hue.From 7 to 8 mm.would be the measurement of the body of the female, including the proboscis.Only males of this species were caught by Loew on the coast of Asia Minor,opposite the island of Rhodes;and he thought it indiginous to Southern Europe.In the summer time,however,Ficalbi captured only females of this species in Tuscany - in the forest of Tombolo near Pisa.As seen by the study of the specimen sent by Ross to Grassi in Rome,the mosquitos with spotted wings,upon which Ross experimented in India,belong to the genus Anopheles,and are very similar to,if not identical with, the Anopheles pictus.Ross distinguishes two varieties - small and large dappled-winged mosquitosIn Italy also there are small and large ones that Grassi regards as different species of Anopheles,distinguishing them not only by their dimensions,but also by the designs on wings and

palpiGrassi calls the large variety, found in Italy, the Anopheles pseudopictus; and it is of about 11 mm. in its entire length. The Anopheles pictus, mentioned above, corresponds to the small form. Very little appears to be known regarding the life and habits of this species of mosquito. The facts observed in the Roman Campagna within recent years refer almost exclusively to the Anopheles claviger, to which appears to belong the chief rôle in the transmission of malaria, at least in such regions. It is the most common and the most numerous of the genus Anopheles in localities of grave malaria therein. In fact, the development of all three varieties of the malarial parasite of man has been observed in this species of mosquito. In addition to the Anopheles, we find in the fields, during spring and summer and autumn, many kinds of mosquito belonging to the genus Culex. But, as the season advances, especially when the temperature begins to be lowered, the Anopheles claviger begins to predominate in the houses, huts, and stables. This is because, with the first advent of cold weather, the fecundated females prepare to hibernate, as nearly all mosquitos do, and take refuge in enclosed places where there are animals and men; these hibernating females become awake, very lively, and sting as usual, when gathered up and taken to laboratories with a temperature of about 68° F. Where the winter season is mild, as on the coast of Southern Italy, we find females of the Anopheles claviger hibernating in caves. The males disappear; and it is evident that only the fertile female hibernates. In the winter the females of Anopheles pictus are to be found in caves in Southern Italy; and they do not appear to hibernate in houses. It is in grottoes, in the trunks of trees, under bushes, etc., that the species of the genus Culex, - e.g., Culex pipiens, - appear by preference to perform this act. Now as soon as the warm weather arrives, the females fly about and sting as usual, and then lay their eggs. Females transported to the laboratory, and kept at a temperature of between 68° and 71° F., laid eggs, as witnessed by Bastianelli and Bignami, in the mohth of March; the larvae were seen a few days later, and developed from fifteen to twenty days. The insect remained in the chrysalis stage for four to five days; thus, after about twenty-five to thirty days in all, the insect emerged from the puparium. The females were seen to have the power of biting and drawing blood in from four to five days after they were born. It is not a difficult matter to distinguish the eggs from those of the Culex pipiens: they are shaped like an elongated spindle with two lateral wings, and are deposited in strings. In each string the individual eggs are placed transversely, and touch each other in the direction of the long axis; they do not therefore have the heaped-up appearance of the Culex pipiens. The larvae are also easily distinguished from those of the Culex pipiens; for they are brown, very agile, and always move in a horizontal direction, never in a vertical or oblique one, as do those of the Culex pipiens. They live in stagnant, preferably in deep, water; and, if the surface of the water be even slightly agitated, they take refuge at the bottom. They are usually found isolated or in small groups, not gathered into large masses like the larvae of the Culex pipiens. They have been seen existing and developing perfectly in very dirty stagnant waters, swarming with every kind of insect life, though Ficalbi affirms that they do not choose

such dirty water as those of the genus Culex frequently do, but often live in clearish water. Herbs supply food for the males; but the females suck blood, and are exceedingly voracious. While we can rarely make an individual of the genus Culex bite by enclosing it in a glass tube, the open end of which is in contact with the human skin, the female of Anopheles clavicer is easily induced to bite under these conditions. They swarm in stables, and attack domestic animals - preferably the horse. + Though some rare individuals appear never to bite, in the case of many members the bite in certain persons produces a persistent wheal which causes the most troublesome itching; but in others, however, the bite leaves no trace at all. They live in the country chiefly, though sometimes they are found in suburban localities. They prefer places where there is plenty of water, and are seldom or never to be found hibernating inside of houses, though they may swarm in the adjoining gardens. The isolated cases of malaria which sometimes are seen to occur in healthy localities may perhaps be explained by the transformation of hay, etc., from unhealthy to healthy localities or towns. The question of their migration is still undecided in other respects. After hibernation the fecundated females seek water, and there deposit their eggs; so that in the spring there are new generations of winged insects. These during the hot season may give rise to several generations. ×

In order to study the development of the malarial parasites of the mosquito, it is necessary to cause adult patients to be bitten by these insects enclosed in glass tubes, the mouths of which are applied to the skin until the enclosed insects have become satisfied. They can then be set free, either under a netting or in a glass jar, in which blades of fresh grass and a few drops of water are placed. The temperature of the atmosphere must be kept at about 86° F. The mid-intestine and salivary glands must now be observed. For this purpose, the mosquito is anaesthetised by ether or the smoke of tobacco, and then fixed upon a piece of coloured glass by means of a needle passed through the thorax, with the back towards the glass; then with a teazing needle we press lightly at about the third abdominal segment, and very gently push apart the two needles, making slight traction, - the entire procedure taking place in a small drop of physiological salt solution, or in one of from 1 to 2 per cent. of formalin. In this way the whole intestine is drawn out; the anterior intestine is ruptured at the thoracic segment, the posterior intestine remains adherent to the last abdominal segments, which are detached from the others, and the all-important middle intestine remains free. To obtain clear preparations of the parasite in the middle intestine, it is well to detach the epithelium before fixation, for examination is naturally interfered with as these cells take on a deep stain. A homogeneous immersion lens is required for the study of the structure of the parasite in preparations that are stained; but for its mere recognition the magnification of an ordinary dry lens will suffice. In dealing with the salivary glands, after fixing the thorax as above, we try to detach the head by slight traction with the needle, and thus sometimes succeed in extracting all the

glandular tubes with their excretory ducts: the anterior half of the thoracic segment must be torn off, with two fine teazing needles, if this does not occur. Having in this way secured fresh preparations, the sodium-chloride or the formalin solution will be required for their study. If stained preparations are required, we leave the same organs adhering to the glass, and fix them with a 5-per-cent. solution of formalin, or a saturated solution of corrosive sublimate; then the specimen is passed through alcohol, and stained by Böhmer's haematoxylin, or by the ferric haematoxylin of Heidenheim. There is, however, another method, from the use of which also a clear idea of the relations of the parasite to the intestine and surrounding parts can be obtained; and it consists in fixing the whole insect in a solution of corrosive sublimate, enclosing it in paraffin, making sections in toto, and staining the same as above described.

The entire process of development of the crescent forms in the body of the Anopheles claviger has been studied by Grassi, and Bignami and Bastianelli; and they have been able to do the same also with the Anopheles bifurcatus and pictus. Ross has seen the first stage of development of the crescents in a form of dappled-winged mosquito, which was recognised by Grassi, in a specimen sent by Ross to Rome, as much like the Anopheles pictus. In Rome it is only in the Anopheles claviger that the complete cycle of development of the parasite has been followed; it was seen to have the characters of a typical sporozoon, after the structure of the parasite had been studied in its various evolutionary phases in stained preparations. From the analogy of similar processes in other sporozoa, we are led to believe that in fertilised crescents nuclear modifications and processes of fecundation must take place, though we have not been able to witness them up to the present. The modifications undergone by crescents in blood taken from man, the formation of the pseudo-flagellate bodies, etc., have already been described; and in doing so, the reasons and data for considering these forms as gametes were stated. We have also observed that the natural medium, in which is completed the formation of the micro-gametes or flagella, and, as we have every reason to suppose, the fecundation occurs, is the mid-intestine of some species of mosquito. By direct research it has, in fact, been established that in the blood contained in the mid-intestine of Anopheles some crescents become flagellated, and even individual flagella have been seen. We do not obtain their regular development (nor do the crescents develop in every case) always when a patient with crescentic forms in the blood is stung by Anopheles. If we examine the middle intestine of an individual of Anopheles claviger, - kept by the thermostat at a constant temperature of 86° F., - a little less than two days after it has sucked in crescent blood, we find in its walls fusiform bodies, which in a fresh preparation appear to be identical in form and appearance with the spindle-shaped bodies found in human blood; they differ from them only in being a little larger, and in having a different arrangement of the pigment. In preparations stained with haematoxylin these bodies exhibit a large nucleus, with a mass of central chromatin, which may be

round or elongated;the protoplasm appears to be vacuolated.More rarely we see pigmented bodies possessing the same characters,but ovoid or roundish in shape.For the most part,the pigment is situated at the periphery of the parasitic bodies;and it is in both spindle and ovoid bodies found to be identical with that of the crescent forms.The seat of the development of these bodies is on the outside of the epithelium and basement membrane between the muscular fibres of the intestinal walls and the adipose tissue thereof;and it is best studied by examination of sections in toto of the mosquito.The parasites will be found to have greatly increased in size on the third and fourth days;and the parasitic body will be seen to have a capsule surrounding it.It now possesses a protoplasm with a reticular aspect,and the pigment is apparently in smaller amount and irregularly disseminated.The capsule is still more visible on the fifth and sixth days;and the parasites themselves have enormously increased in size - up to 70 mm.or more.They project from the walls of the intestine into the coeloma,and may easily be seen - even with a low power of the microscope.In their interior may be seen shining bodies resembling fat,which in part existed in the previous phase;and numerous small bodies, which in stained preparations are recognised as nuclei. Looking at the parasite on the seventh day,it appears to contain an enormous number of delicate,thread-like filaments with thinned extremities,about 14 mm.in length,arranged like rays around one or more homogeneous masses,in which a little black pigment is still to be seen.Exit is give to innumerable filaments,- in the centre of which will be seen one or more granules or small bodies of nuclear chromatin in preparations stained with haematoxylin or after Romanowsky's method,- if they are crushed in such a way as to break the capsule.The developing stages,which go on to maturation,are evidently represented by the individual forms so far described - i.e.,of a sporozoon.This development consists essentially in an increase in size with encapsulation;and in successive multiplications of the nucleus,up to the formation of very small nuclei,around each of which is gathered a little protoplasm - the spotoblast without capsule.The sporoblasts are transformed into the filiform elements described - the sporozoites;so that the mature sporozoon on the seventh day is composed of the residue of segmentation and a thin capsule with innumerable sporozoites.The torn and flaccid capsular membrane in the succeeding days is found to be adhering to the intestine,and near to it the sporozoites,which later accumulate in great number in the tubules of the salivary gland,or within the cells of this gland,or in the glandular lumen.It has been repeatedly demonstrated by experiment that at this point the Anopheles,biting a healthy man,inoculate him with the sporozoites along with the saliva,thus determining an aestivo-autumnal fever,after a period of incubation.The temperature appears to have a certain influence upon the time required for the completion of the life cycle in the Anopheles claviger.The development does not seem to occur at all at a temperature of from 57 to 59 F.,and at from 68 to 71.6 F.it is much slower than that which has been described.It must also be noted that we may find,in addition to the forms described,in the mid-intestine,within the

capsule,peculiar brown bodies,varying in size and irregular in shape,some like rods,others ovoid or round, some straight and other curved.The retrogressive changes in the sporozoa are supposed to give rise to these bodies;and this because of their irregularity and their sometimes stratified appearance.They,are like the bodies seen by Ross in studying the Proteosoma coccidia ,may be found within broken or shrunken capsules,or else within a large capsule,which is apparently distended by its contents.

Grassi,and Bignami and Bastianelli have studied the development,in the Anopheles claviger and bifurcatus, of the large pigmented bodies of the tertian parasites; and the two last-mentioned observers have traced the entire life cycle of the parasite in question in the latter insect.The formation of the macro- and the microgametes has been described already,as also their structure;and we have seen that the ulterior life phases of these bodies are normally developed in the mid-intestine of the Anopheles.Here occurs the fertilisation of the macrogamete by a flagellum or microgamete;and the fecundated body then penetrates into the intestinal wall where it continues its development.As before mentioned, the theory that the sporozoon developed in the Anopheles is the fecundated macrogamete is founded upon analogy;for,up to the present time,no one appears to have had the opportunity of actually witnessing the process of fecundation,nor of following the first succeeding nuclear changes.We can easily see a certain number of tertain bodies in the thickness of the walls of the middle intestine,especially in its terminal portion,in the case of Anopheles which have bitten a tertain patient having in his blood the forms regarded as gametes,and which are kept,for about forty hours after the punture,in a constant temperature of about 86°F. They appear as round,pigmented bodies,very transparent, and with distinct outlines,and contents varying in appearance - sometimes uniform,sometimes vacuolated,or else divided into masses.They are easily recognised by the characteristics of the pigment,which are those typical of the tertian pigment,which is usually immotile, and only exceptionally in motion.In preparations stained with haematoxylin we see that the protoplasm has a reticular appearance,and that the chromatin has increased in amount,- relatively to the amount seen in the same bodies before they have penetrated the intestinal wall,- and not rarely it is undergoing division or had divided into various little masses.The diameter is one and one-half to two times that of a red blood-corpuscle at this stage of development.The parasites are seen to be from one-fourth to one-third larger on the third day than on the second.They posses a very evident cystic wall; and in fresh preparations their contents are seen usually to be divided into little masses,between which is the pigment.A varying number - from eight to fifteen - of round,ovoid,and deeply coloured nuclei are to be found in stained preparations.The cyst wall is very distinct,and the size of the cystic body has increased about one-fourth,on the fourth day.The protoplasm preserves a reticular,almost spongy,appearance;and the nuclei are more numerous - twenty to thirty - and somewhat smaller than in the preceding stage.The parasites,- which from the beginning have been

situated outside of the intestinal mucous membrane, between the fibres of its walls,- between the fourth and fifth days, begin to project between the fat cells into the coeloma. They continue to increase in size, so that they are easily visible with a low power of the microscope. In fresh preparations they look like the bodies of the preceding stage; and in stained preparations the nuclear division is seen to continue, so that more numerous and smaller nuclei are formed. Filaments or sporozoites,- arranged side by side like a palisade, and in groups around masses of an apparently amorphous substance,- are, as a rule, seen within the capsule on the third day. The presence of amorphous masses,- which are usually multiple, and which represent the residua of segmentation,- are seen in stained preparations; but at this time some capsules in fresh preparations appear to be almost filled with sporozoites. Our description of the mature sporozoa of crescent origin applies to the structure of the sporozoites. It must be remembered, however, that the description in question is somewhat schematic as regards the size of the body and the stage of development in the several days after the puncture. We may, in fact, observe cystic bodies, about as large as those of the fourth day, already mature, that is to say, filled completely filled with fully developed sporozoites. Furthermore, cystic bodies, of various sizes and in different stages of development, are often seen in mosquitoes which have bitten a patient only once. From this it follows, then, that the development of the malarial parasites does not occur with the same regularity as to time in the intestines of the Anopheles as it does in the blood of the human subject. The brown bodies described by Ross in the so-called proteosoma coccidia, and found in Rome in the crescent sporozoites, have not been found in mosquitos nourished with tertian blood. The broken and shrunken capsules, after about the seventh day, have been found in the intestines and the sporozoites in the cells or the excretory ducts of the salivary glands. The sporozoites are either of the form they are in the capsule in the intestine, or else short and thick in the latter.

Bignami and Bastianelli affirm that the following are the differences between the crescent and the tertian sporozoa in the anophelic life cycle, which, though slight, admit of a differential diagnosis in some stages of development at least: First, In the tertian sporozoon the sporozoites are less dense and more regularly arranged, sometimes in rays around the residua of segmentation, than in the capsule of crescent origin. Though there are mature capsules which exhibit no appreciable differences, the residua of segmentation in the case of the tertian parasites are usually composed of several granular blocks, which are more numerous than in the case of crescent parasites. Second, in the crescent the form of the sporozoon in the first stages of development is either spindle or ovoid,- in the rare cases in which it is oval, this may possibly be due to stretching during extraction from the intestines,- while in the tertian it is round, or, as just parenthetically expressed, oval. Third, at the same stage of development the crescent sporozoon has a more distinct outline and greater

refractive power;so that,while the tertian is more transparent and in the first stages is visible only by a homogeneous high-power immersion lens,it is well seen even under a low power.Fourth,the quality of the pigment is naturally identical with that of the corresponding parasites in the human being.Fifth,and finally,the nuclei of the tertian sporozoon are less numerous and larger than those of the crescent sporozoon at the same stage of development -i.e.,after successive divisions.

Numerous experiments have been from time to time conducted as to the development of the quartan parasite in Anopheles claviger,but seldom with a positive result.In one Anopheles claviger norished upon a woman who had suffered for eighteen months from quartan fever, and who had many parasites in the blood with a few rare gametes,there were found two capsules containing the characteristic pigment of the quartan parasite.These capsules,when three days old,had about the same dimensions as the two-day capsules of crescent origin.The negative results obtained in so many researches are probably due to the extreme rarity with which flagellated bodies are found in quartan blood.It is possible that in this species of infection,in which the parasites grow so flourishingly in human blood,there may be so complete an adaptation of the parasite to this mode of existence that after a while it may entirely lose the power of producing bodies capable of ulterior development in a different atmosphere.It appears - from the most recent researches made by Bignami and Bastianelli,who have succeeded in observing the whole life cycle of the quartan parasite in Anopheles claviger - that positive results are obtained only in cases which have lasted a very long time;that only in cases which have had several relapses do the gametes make their appearance;and that the results are negative when recent cases are employed for experiment.

Many authors have affirmed that it is possible that there may be other life cycles;and that the forms described above for the crescent and tertian parasites represent only the life cycle of these beings.In addition to the forms already mentioned,some writers have noted,in relation to the development of the crescents in Anopheles claviger, tubular or ampulla-like masses of small round or oval bodies,some hyaline, others covered with a dark yellowish-brown membrane;in the same preparation,indeed,we may see the various phases of development of thick membrane which surrounds the hyaline body.These bodies,which are found within the intestine or in the dorsal vessel,appear to be resistant spores;and,as they greatly resemble the brown bodies of unknown significance which are found within the capsule of malarial sporozoa,the authors whom we have quoted,at the beginning of their researches, held that they were identical with these brown bodies, and considered them to be a resistant form of the malarial parasite in the mosquito - a form capable of passing into water at the insect's death,and then going through with a new life cycle.Later researches, however,have demonstrated that the development of the

brown spores,from the typical forms of malarial sporozoa, cannot be followed;they then held that these were special parasites,probably another parasitic sporozoon of the Anopheles having no relation to the malarial parasite.No known form of the malarial sporozoa of the mosquito,possessed of the significance of a resistant spore,has therefore as yet been observed.The hypothesis that the malarial parasites,through the eggs and larvae,pass from the infected mosquito to its progeny has derived the semblance of probability from what is known of the biology of the parasites in Texas fever; and an attempt has been made to solve the question in regard to the parasites of human malaria by two methods of research.On the one hand,the eggs and larvae of supposedly infected Anopheles were studied;and,on the other hand,men were caused to be bitten by mosquitos born in the laboratory,and which were therefore known not to have been nourished by malarial blood - to ascertain whether they bore in themselves germs of infection from their birth being the object of such experimentation.The former class of researches resulted in the fact that in the well-developed eggs of the Anopheles there were not infrequently found cystic bodies containing eight easily coloured little bodies, which may be considered as the spores of a sporozoon with eight sporozoites.But it has not been possible to determine whehther there is any relation between these bodies and the malarial parasites:in fact,it would seem that there is none.On the other hand,no forms at all like the malarial parasites have been found in newborn mosquitos;neither has it been possible to follow the development of these bodies in the larvae.Entirely negative results have also been given by the second class of experiments.Of the numerous healthy persons who allowed themselves to be bitten in the laboratory not one took the fever.The subject is still being investigated in various quarters.The only deduction that we can make so far is that the malarial parasites pass from the sick person into certain species of mosquitos,and from these,after having pursued the life cycle described,they return again to man.

Malarial Environment.

Malaria has in some localities prevailed for hundreds of years, though in others there have been endemics and epidemics observed. Such predispositions Celli terms the "localistic predisposing causes."

DISTRIBUTION OF MALARIA.

The disease occurs in almost all parts of the world; and there are few diseases which have so wide a distribution. As stated, there are, however, certain principal foci where the disease is permanently endemic. These regions are chiefly in the warmer temperate and tropical countries. Generally speaking, the farther one departs from the equator the less common are the malarial fevers. A sharp line of delimitation cannot, however, be drawn. Occasionally cases have, according to Celli (Verhandl. d. X. Internat. Med. Congr., Bd. 5, Abth. xv, p. 68), been observed as far north as Irkutsk in Siberia, Hapanandra in the Gulf of Bothnia (65° N. latitude), Juliushaab, Southern Greenland, and New Archangel in Alaska, while to the south malaria has been reported to exist as far as the isotherm of 60°. It must, however, be remembered, in considering any statistics concerning the distribution of malaria, that the diagnosis of malarial fever has been, until comparatively recently, - and is, unfortunately, far too frequently today, - made upon a very insufficient basis. In many regions at the present time an intermittent fever with chills is without further investigation assumed to be of malarial origin; and even at the present time, in some of the large cities and towns abroad, there are statistics which are absolutely incorrect showing thousands of deaths from the disease every year. All are agreed, however, as to the principal haunts of malaria. In Europe the disease is common in the low lands about the coasts of Italy, Sicily, Corsica, Greece, the Black and Caspian Seas, and the Volga. About the coast of certain parts of France, Spain, and in Denmark and Sweden, an occasional case is seen. In Holland and Belgium the milder forms of the disease are not uncommon; while a few cases of the same nature are seen in Germany about the north of the Elbe and Along the Baltic coast of Prussia, in Silesia, the plain of the river Mark, and in Pomerania. In tropical Africa the disease appears in its most severe forms, especially along the West Coast. The chief foci of the disease in Europe are Italy and Southern Russia. In India, Ceylon, and in the East Indies it is particularly common, while in Southern and Southwestern China it is also endemic. In Japan the disease is rare. In the Western Hemisphere malaria is seen in the lowlands about the coast from New England to Florida, though above Virginia the severe forms are rare. In the Gulf States and along the banks of the Mississippi and its tributaries, in most of the Southern States, the disease is almost always present. About some of the Great Lakes, both in the United States and in Canada, malarial fevers are occasionally seen; while from the Pacific coast a certain number of cases are from time to time reported. Some of the most fatal cases of the disease are to be encountered in Central America, Mexico, and Cuba. The dreaded Chagres fever of the Isthmus of Panama is a

pernicious malarial infection. About the lowlands of the eastern coast of South America, particularly in the Guianas and in Brazil, the disease is endemic in its most malignant forms. On the west coast it is less frequent, though its occurrence in Peru and Bolivia has been known for years. Indeed, it is from the Peruvian Indians that we learned the value of the specific remedy for the disease. In Australia, New Caledonia, and the islands of the Pacific the disease is very rare; and, notwithstanding the existence of extensive low marshy tracts, it is quite unknown in some regions - such as Hawaii, Samoa, New Zealand, and Van Diemen's Land. The infection may often be traced to a previous sojourn in a malarious district in cases of malarial fever which occur sporadically in regions where the disease is uncommon. Extensive epidemics and pandemics of malarial fever, spreading over the greater part of the world, have been described. The true natire of the affection, however, in most of these instances admits of considerable undertainty.

PHYSICAL GEOGRAPHY.

The prevalence of malarial fever is rather considerably influenced by the physical geography of the dountry. According to Laveran, the "principal foyers of paludism are situated on the coast or along the banks of large rivers". High altitudes are usually free from malarial fever, and the mountains and plateaus in the neighbourhood of malarial districts are often used by the inhabitants as sanitaria. The high altitudes may not, however, be a protection, as fevers occur in the Tuscan Apennines at a height of 1100 feet, in the Pyrenees at 5000 feet, on the island of Ceylon at 6500 feet, and in Perus at from 10,000 to 11,000 feet. It is, however, by no means improbable that many of these fevers which have been called "malarial", - as in the case of the "mountain fever" of the Western States, which is for the most part, probably, enteric fever, - are, in reality of some other nature.

THE SOIL.

For a great many years malaria was held to be of telluric origin, and that the pathogenic germ rose into the air from the soil and from stagnant pools of water; and this belief gave origin to the study of the soil in malarious regions, a study which was prosecuted in all directions. The endeavour mas made to discover in what way the malarial germs were carried a certain distance above the ground, especially at certain hours; the geological nature of the soil in places where malaria exists was determined, and a search was made in the ground for the malarial parasite. As argillaceous, calcareous, and even granite soils may be found in malarious localities, the geology of an infected district is not of any importance. It is not the nature of the soil that exerts an influence in the production of malaria, but the fact that beneath a more or less thick stratum of humus there is an impervious layer, for example, of calcareous tufa, marl, or clay; the consequence of this is that the soil is permanently moist, and there is a layer of water at the bottom of the permeable layer, while there are pools formed in the depressions of the surface. In the

Roman Campagna,for example,such conditions exist.To demonstrate the importance of this factor we may recall the example given by Meunier of what took place when the necessary evacuations were made for the railway from Madrid to the Escurial.For a distance of fifty kilometres from Madrid no cases of fever occurred among the labourers,but in the construction of the second half of the line the workmen suffered severely from malaria. There was no difference whatever in the hygienic conditions,but there was a difference in the nature of the soil,which was for the first half diluvial and sandy, but for the second half of the distance granitic and schistous.The fact that malarial endemics exist by preference in low marshy places,in the deltas of large rivers,in the broad alluvial plains bordering wide rivers,and in valleys in which are swamps and watercourses may be taken as proof that malarial fever is related to the humidity of the soil and to the presence in it of collections of water.The presence of marshes were held to be of great importance by the physicians of former times;and Lancisi recognised as the only cause of intermittent fevers the noxious effluvia rising from swamps.He made a distinction between noxious marshes and those of a harmless character.The noxious swamps were those of wide extent and shallow,in which,although there might here and there be an intermittent current, for the great part of their circumference,especially when the banks were flat and covered with rank vegetation,the water was stagnant;it was from the death and decomposition of the myriads of insects and of the marshy vegetation that the noxious effluvia arose.The harmless bogs were those in which the water,either fresh or salt,was for the most part deep,in constant motion,containing little slime,with many fish,and especially if the banks were high and not grown over with canes and weeds.Lancisi says that he has seen malarial endemics disappear after the drying up of bogs.He records an instance in point:As a sequence of the formation of a marsh,in Rome in the Celimontana valley near the church of San Giovanni in Laterano, there occurred an endemic of fever and a plague of mosquitos,and in the neighbouring hospital of San Giovanni there were several cases of pernicious fever that summer;but when the marsh was filled up,by his orders,the endemic ceased in a short time.As there are marshy places where malaria does not exist,and malarious districts which are not swampy,it is not correct to assume that the presence of marshes and the occurrence of malaria are two closely connected facts,although swamps are not infrequently found in malarious places. If,as Tommasi-Crudeli observes,the malaria in the Roman Campagna were dependent upon the presence of swamps,it would prevail over a very limited area.But the same author remarks that,in the malarious districts where no swamps exist,there are to be found many collections of water,little ponds and pools all about, fed by the rains or by the subsoil water.These collections of water are more than sufficient for the development of mosquitos,especially the malarial varieties, which require pools surrounded with vegetation for their support.The prevalence of malaria may be favoured,

in addition to these swamps, stagnant pools, etc., by the presence of rice-fields, of places where hemp is macerated, and of ponds on the seashore where the salt water is mixed with the fresh. Even the irrigation of cultivated fields may be a cause of malaria; and the history of irrigation in Southern California has made it plain that if irrigation works are not to become producers of malaria, drainage must proceed pari passu with the irrigation: malaria is very prevalent when this is not done. Indeed, efficient drainage of marshy districts which have been rich in malarial fevers has a marked effect upon the frequency and severity of the manifestations of the disease. Years ago, malaria was common in the surroundings of London, which were marshy and ill-drained; today, thanks to good drainage, the disease is there unknown. The effect of good drainage upon the Roman Campagna has been very striking, the severity of malarial fever diminishing rapidly. The low lands of Holland used to be the seat of very severe malaria: today, only occasional cases of the mildest forms of the disease occur. A malarial endemic may be produced by anything which results in the formation of pools of stagnant water - such as inundations, the denudation of hills, ploughing, and, in general, any upturning of the soil in the construction of railroads, canals, fortifications, diking of rivers, etc. Inundations have sometimes been followed by a recrudescence of malaria in places where the disease had formerly existed. Frerichs, in 1854, observed an endemic of grave and even pernicious fever, following an overflow of the river Oder in Silesia, where previously only mild cases of malaria had existed. Although it is true that the felling of timber in the plains may contribute to the sanitation of such places, the same thing in uplands may, in consequence of hydraulic disturbances thereby produced, be a caise of aggravation of malarial endemics. According to Pellarin, - who is cited by Rho, - in the island of Mauritius, where, after the denudation of the hills, the little mountain torrents, which formerly ran down to the sea, now disappeared on the way and ended in pools of stagnant water, while in the rainy season they often overflowed the same country, forming temporary marshes. Coincident with these telluric changes the malaria on the island became more widely spread and graver, and cases of pernicious infection occurred. Some years ago, an endemic of malaria occurred in the Trastevre quarter of Rome when the works preliminary to the banking of the Tiber were begun. Even the works undertaken for sanitary and economic purposes may be the cause of an outbreak of malaria, or of an aggravation of the already existing endemic. There are many cases on record in which the denudation of a soil covered with forests or rank vegetation, or the turning up of the soil in a district which was previously free from the disease, may be followed by an outbreak of malarial fever; while in other regions where the disease already exists, similar interference with the vegetation or the soil may greatly intensify the severity of the process. An example of this latter condition is shown in the severe outbreak of malarial fever which was associated with the excavation of the Panama canal.

In Paris,which for many years had been free from palludism,the digging of the Canal Saint Martin,and,again, in 1840,the excavations of the fortifications,were,in each instance,followed by an outbreak of characteristic intermittent fever.Irrigation of low lying districts without proper drainage,- for example,in some of the irrigated districts in California,- has been followed by an outbreak of malaria or an increase in the severity of the cases.The disease is said to prevail mainly in plains and valleys;and it appears that the frequency of its occurrence diminishes with the elevation above the level of the sea;and even immediately above plains made desolate by malaria,salubrious regions are often found. For instance,the district of Norma,on an abrupt rocky elevation about 1500 feet above the Pontine marshes, enjoys a most salubrious atmosphere.Nevertheless,as already stated,malaria may exist in the mountains;for example,on the eastern slope of the Rocky Mountains it is found at an elevation of 6500 feet,and in the Peruvian Andes at 8125 feet.Grassi has seen a malarious district near Colico at a height of 8450 feet;and the disease has been observed ay considerable elevations in other parts of Italy.The literature of malaria afford numerous examples of circumscribed endemics of that affection.One of the best known is that which occurred near the city of Senegallia on the Adriatic.In this city,which is famous for its beautiful shores and for the magnificent hills about it,in which are schools, hospitals,and other public institutions,and which is visited in the summer by crowds of bathers,malaria is unknown,as it is als o in the surrounding country,as well as in the neighbouring hills where there are numerous cottages,villas,and houses inhabited the entire year.But there is here one very limited area of malaria,which is quite grave because of the number of cases,as well as of the severity of the disease in those attacked.This endemic is situated without the walls in a little suburb consisting of a row of houses,in some places double,along the left bank of a large drainage canal,constructed for the purpose of carrying off the excess of water coming from the hills,and conducting to the sea the overflow from the river Misa.During the hot season the flow of water in this canal ceases;but,in consequence of irregularities in its bed and banks, there remain numerous pools and stretches of stagnant water,the surface of which is covered with aquatic plants.The canal is deep,and in the upper parts its irregular banks are covered with vegetation,while in the lower part its bed widens out as it nears the sea. Spanning the canal are four bridges,the one nearest the sea being for the railroad.Now,the malarial endemic is confined to the houses situated along the upper part of the canal,very many of the inhabitants of which are sufferers from malaria,those sleeping in the lower stories being first attacked and those in the upper rooms, whose windows look out on the canal,next.This last-mentioned fact is particularly noteworthy,as no cases of malaria were found among those who lived in the upper rooms facing the street which runs parallel behind the first row of houses.Furthermore,it is interesting to observe that a family of six persons occupying the upper story of one of the houses on the bank

of the canal, the windows of which, however, looked on the street, had remained free from the disease; but, early in August, 1897, this family was obliged to remove to the lower floor of the same house, on the canal side, and, after having been there for fifteen days, every one of the six members of the upper rooms which had been vacated by this family continued to be in a healthy condition. At some points the houses along the canal formed a double row, while at others there is but a single row, this being sometimes on the canal side of the street, sometimes on the other side. Now, where the row on the canal side is interrupted, the inhabitants of the other row suffer from malaria, but there are no cases to be found, where there are houses in rows on both sides, amongst those in the dwellings on the farther side. There are, with the exception of the houses mentioned, others visited with malaria either in the surrounding country, or in the city or in the hills; and even, as just mentioned, there is no malaria in the rooms of the houses along the canal the windows of which look out on the street behind. There is also no malaria in the houses along the lower part of the canal where the sea enters for a short distance; indeed, some of these latter houses are even rented by the summer visitors. Along the railroad, as well as among the labourers in a large sugar refinery, the disease does not exist. In the case of this well-defined endemic, malaria occurs in all its forms. In the spring we find only the distinctly intermittent fevers, especially tertian; but in the summer and autumn the aestivo-autumnal infection predominates, and cases of pernicious fever also occur; in winter there are the relapses, the anaemic and other sequelae of infection. The presence of various species of malarial parasites, corresponding to the clinical forms observed, is revealed by microscopical examination. The various febrile types are encountered amongst those occupying the same house, and even the same room. It is clearly evident from this description of such a markedly circumscribed endemic of malaria, in which we find all the forms of infection, - as also in other centres of grave malaria, the Pontine marshes, for example, - what are the telluric conditions necessary to its development and maintenance. These conditions consist in the formation, during the summer, in the bed and banks of a canal, of small collections of stagnant water covered with a layer of vegetation, surrounded by mud and shaded by the rank vegetation of its banks. Here are no extensive marshes, nor even stagnant ponds, but only puddles in which plant decomposition takes place. Now, in these stagnant pools the larvae and nymphae of the mosquitos, which infest the houses of the wretched sufferers from the fever, find a suitable nest. That the telluric conditions mentioned were the true determining cause of the malaria was demonstrated by the fact that this latter, running into the autumn of 1897, did not reappear in the summer of 1898 when these conditions had been removed by a process of natural sanitation. Torrential rains and floods occurred during the autumn of 1897 throughout that region, carrying away much of the sediment in the canal, deepening it by from two to five yards, and uncovering the timbers of the old bed; the flood also wore away the banks smooth, and even undermined some of the houses. The consequence of this was that, in the summer of

1898, the water of the sea entered the canal which was kept clear by the ebb and flow of the tide. Not a single case of malaria occurred among the occupants of the houses infested by the fever during the previous years; the mosquitos almost entirely disappeared, and it was only specimens of Culex that were to be seen. Another very important fact is forthcoming from the study of this circumscribed endemic, namely, that endemic malaria remains fixed in the place where the telluric conditions are favourable, and does not spread to any distance, even horizontally. Indeed, this intense and grave malarial endemic was confined for years and years to the few houses whose doors and windows looked out on the upper portion of the canal, where the stagnant pools were located. One gate of the city is but a short distance from the canal; and from the same part is seen one of the bridges crossing it. Immediately within the gate is an asylum, the hospital, and many houses, in all of which malaria is unknown; and of the city guards, who are stationed at the gate from early morning to late in the evening, none can be found who has ever suffered from intermittent fever. It is evident from this that malaria is not carried by the winds, but that it is joined to the conditions of the place where it is located. Furthermore, as those who suffered at Senigallia drank the same water as the occupiers of the immune houses, it is evident that the drinking-water cannot be the vehicle of infection. Guided by the two great discoveries,- that of the parasite in the blood, and that of the malarial mosquitos,- not only is it possible to study more accurately the endemiology and geographical distribution of malaria, but pandemics of the disease will be better understood than heretofore, and the reason for the affection being unknown in certain places where all the conditions favourable to its development appear to exist. The study of the meteorological and telluric conditions existing in places devastated by malaria, especially of the second named, will be much easier in the future than in the past; for, as it is now known that the malarial parasite does not live free in the soil, but that it enters the bodies of certain species of mosquitos, the problem will be greatly simplified. Finally the cultivation of many marshy, malarious districts has been followed by a marked improvement in the sanitary condition. The planting of trees has been supposed to have a particularly good effect, possibly because of the drainage of the soil which is thus accomplished. For some time it was supposed that certain trees - particularly the eucalyptus globulus - had an almost specific effect in protecting the neighbourhood against malarial fever. The advantages of this particular tree have, however, been much exaggerated. Malarial fever never originates at sea. Those cases which have been reported date their infection, unquestionably, to some period before the voyage.

CLIMATE.

For the development of malaria heat is one of the factors of cardinal importance. This is evident when we consider that the disease rarely extends beyond 63° to 64° of north latitude, and 57° south latitude; and that, in proportion as we pass from these limits towards the equator, the disease progressively increases in both

prevalence and virulence.Hirsch sought to determine exactly the northern limit of malaria,but found in individual malarious centres great differences in temperature and latitude,and demonstrated that it was not the mean annual temperature that should be taken into account,but the mean summer heat.It is between the isothermal lines of 59° and 60.8°F.that he places the northern limits of the disease.The significance of temperature is also apparent from the fact that,while malaria in the tropics where it prevails endemically presents mere oscillations in relation particularly with the dry and rainy seasons,in temperate regions it is especially in the summer and autumn that the disease prevails;and,again,in those parts where all the varieties of malaria are found it is only at these seasons that we see the grave and pernicious forms of the disease.Thus,in the malarious parts of the Roman Campagna malaria occurs only in its milder forms - chiefly simple tertian - in the spring,while the grave forms constituting the aestivo-autumnal endemic begin after the first extreme heat of summer,usually in the month of July,and continue with oscillations during the summer and autumn,the endemic being more or less prolonged according as the cold comes late or early,but usually ceasing abruptly about the end of December.In winter we observe relapses of the infection contracted in the summer and autumn;and these,though they occasionally continue until summer,usually grow milder and milder and cease,as a rule,in the spring.The last cases of primary attacks observed at the end of the season of malaria may not declare themselves for many days after the possinility of infection has passes;and the cases in which a primary febrile paroxysm occurs after the first frost can be explained in this way.Mal-

SEASON.

Malaria exists usually throughout the year in tropical countries,but it is almost always more severe in the summer and autumn.As one approaches the temperate climes the cases in winter and spring become very rare. Along the eastern coast of the United States of America, just as in Rome,the cases in the winter are very few, while with the spring a certain number of infections begin to appear;it is not,however,until July that the real malarial season begins,its height being reached in the months of August,September,and October.The variations in the occurrence of the disease according to the season of the year is well instanced by the number of cases treated at the Johns Hopkins Hospital between January 1, 1890,and January 1,1894:In January there were 9 cases; 8 in February;the same number in March;17 in April;21 in May;18 in June;38 in July;66 in August;122 in September;120 in October;38 in November;and 25 in December - making a total of 490 for the twelve months in question. The mildest types of infection are seen in the earliest cases.Thus,in the spring the first cases are usually tertian or quartan infections.As the season advances, double tertian infections become more frequent,while at the height of the season the majority of cases are of the aetivo-autumnal type - the most severe form of malaria.This observation of the variation of the types

of the fever is a very old one.It has long been supposed that the early cases of fever in the winter and in the spring represent,in toto,relapses from infections of the preceding autumn,the fevers of first invasion beginning only with the summer months.Various analyses of cases have shown,however,that,while the proportion of fevers of first invasion is less in the spring than in the summer months,yet they do occur at that period.Dr. Ballori has drawn up a table,showing the number of patients with malaria received each month during the years 1889-96 in the Santo Spirito Hospital at Rome,from which the close dependance of the malarial infection upon the seasons is apparent.It demonstrates that most of the cases of the disease occur in the months of July,August,September,October,and November.In December the number of those received for malaria is markedly less,and continues to decrease progfessively through the winter,during which time only patients with relapses are received.In the months of May and June there is a more or less noticeable increase marking the spring endemic,but there is a striking and sudden increase, denoting the beginning of the aestivo-autumnal endemic, in July.It is not,however,everywhere that this ralation between the number of cases and the months of the year is to be observed.In some malarious districts in Italy the maximum of the aestivo-autumnal endemic occurs in the autumn,especially in September and October,and in other places even in November and December.Furthermore, in the same place the period of maximum prevalence may vary in different years.In the Roman Campagna,in the year 1898,it was in November and December,and even in the first part of January,that the greatest number of pernicious fevers occurred.The effect of heat,however, does not declare itself immediately;and there are other intermediate factors concurring in the production of the disease.Thus,while it is certain that the aestivo-autumnal endemic always develops after the first strong heats of summer,it is also certain that it may be prolonged in the late autumn when the temperature is lower than that of June in which few or no cases of primary aestivo-autumnal infection are seen.Furthermore,the gravity of the malarial endemic in any year is not always in direct ratio with the height of the mean temperature for the warm months.The latter may even be lower than usual and the former extremely severe.The life of the malarial mosquitos has to do with this course of the malarial endemic relative to the seasons. With the first intense cold some of the mosquitos die, others hibernate.In the spring the latter emerge from their hiding places,and deposit in stagnant water their eggs,whence come the new generations to which others succeed in the summer and autumn.Researches are still being carried out with the view of discovering the relationship between the development of aestivo-autumnal endemic and what happens to the mosquitos whereby they become infected.It is now known that in the late autumn the malarial mosquitos,very many of which are infected, seek shelter in the houses.The curious fact of there being true house epidemics of the disease,and the great liability to infection at this time can thereby be

explained.The origin of the aestivo-autumnal endemic is not yet understood;but doubtless we shall soon know is the daughter mosquitos have inherited from their mothers the infection which requires an elevated temperature in order to develop and be transmissible to man;if the daughter mosquitos infect themselves by sucking blood still containing crescent forms,and if these develop in them later when the temperature of the air permits;and also if the mosquitos become infected in some other way,as.for example,by sucking the blood of other animals. The possibility of a seasonal polymorphism of the haemosporidia of human malaria,- that is to say,of the transformation of the spring parasites into aestivo-autumnal ones,- has been suggested by various observers.

RAIN.

Thus appears to have an important influence upon the production of the disease.In tropical countries, where the rainy season alternates with the dry,we find the curve of malarial morbidity corresponds very nearly to that of the rainfall,and in such a way that the maxima of the first follow those of the second at an interval of about a month.It is the general belief that in climates that are temperate an injurious influence is exerted by the summer and autumn rains;and also that a very rainy spring is followed by a malarial season, more serious than usual - by reason both of the number of cases and their gravity.Rain appears to influence the development by acting as an occasional exciting cause of the development of the infection in the human being,and also by favouring the telluric conditions necessary to the production of the disease,or,more exactly,of the life of the mosquito.It is by the heavy rains of the spring that there are formed numerous stagnant pools and marshes where the mosquitos can deposit their eggs;and similarly the rains of the summer and autumn keep these pools and swampy places from drying up.But the amount of rain must not exceed a certain limit;for,when heavy showers follow each other at short intervals,the exit of the winged insect from the puparium may be prevented.Furthermore,the influence of rain may be,as regards its influence in the production of malaria,be nullified by several factors,as,for example,when a strong wind is blowing in the intervals of the showers so as to dry the soil quickly.To this action of rain we may add another,namely,that of favouring the manifestation of the infection in a person who already has the germ in his body.This second effect of rain is manifested very quickly,while the first-mentioned requires considerable time:a month,according to experiments in hot countries,which is a period corresponding to the incibatory stage plus the aquatic life of the mosquito.

WINDS.

There is much that has been brought forward to suggest that the infective agent of malaria may be carried by the wind;but all are not agreed as to this probability.Some have affirmed that the disease may be transported long distances,even from one continent to another across the sea,by the agency of the wind;but others strongly object to this hypothesis,and others, again,look upon the wind as actually doing good by dispersing and destroying the malarial germs.The first of these opinions if held by Lancisi,who,in accordance

with this belief,would not permit the cutting down of groves,even in the plains,maintaining that they acted as filters purifying the air passing through them of the emanations from marshes.But this view is opposed by so many and such convincing facts,related by numerous observers,that we can no longer admit any connection between the winds and the diffusion of malaria.It is sufficient to recall the fact that on ships anchored even close to the shore of exceedingly malarious districts,the members of the crew never suffer from malaria so long as they remain on board the vessel,but that many acquire the disease,and perhaps succomb to it,if they go ashore and remain even for a single night.For instance,Mannaberg says that Vincent and Burot affirm that in the Madagascar campaign of 1895,while the French troops were deceminated by the fevers,the sailors who remained for months on board the ships,hardly three hundred yards from the shore,escaped. Then,again,in very circumscribed malarious districts the infection may be intense,but it will remain within these narrow limits for years and years without spreading itself in any direction;in cities like Rome,situated in the midst of an eminently malarious region,even during the season,when numerous malarial cases as admitted from the neighbouring Campagna to the hospitals,the inhabitants never contract the disease.Why malaria cannot be transported by the wind can,as a rule,be explained,if it is true that man acquires the disease only through inoculation by infected mosquitos,by the habits of the latter.For,as a matter of fact,when the wind blows the mosquitos conceal themselves in the grass or on the leaves of the bushes,and only when the wind dies down in the evening do they take wing,sting men and animals, and invade the houses.Furthermore,in no single instance were any species of Anopheles found after repeated and careful search in the gardens,within the city of Rome, situated at a very short distance from the malarial Campagna;and the observations of Grassi demonstrate positively that malarial mosquitos are not transported by the wind,for he found Anopheles in circumscribed malarious districts,but was unable to discover any at all in neighbouring regions that were free from that febrile affection.

ALTITUDE.

Time out of number it has been observed in malarious districts that the dangers of infection are much greater close to the ground.Sleeping upon the ground is held to be particularly dangerous in such localities.

TIME.

It is said that infection takes place more readily by night than by day in infected districts.

DRINKING WATER.

As a source of malaria many have laid,and still do, great stress upon drinking-water.The experiments,however, of Celli,Marino,and Zeri,who caused individuals to drink in large quantities water which was obtained from the most malarious districts,without any bad effects,and of Grassi and Feletti,who fed individuals upon dew collected from malarious regions,with similar negative results, are strong arguments against this idea.

OCCUPATION.

The susceptibility to malaria is considerably influenced by occupation. Soldiers and tramps who sleep upon the ground in malarious districts are particulary prone to contract the infection. While those whose work takes them into the insalubrious country are apt to take the disease, labourers in the cities are exempt, with the exception of those who live in houses on the outskirts of the city overlooking the open country. But even among the field labourers we must distinguish between those who remain in the country only during the day time and those who pass the nights there, the latter being more subject to to malarial attacks; also between those who work only in the winter and spring, who do not take the disease or only in a mild form, and those who toil in the fields during the summer and autumn, who suffer more frequently and often from the pernicious fevers. In the Roman Campagna, for example, the labourers who harvest the hay in the spring are free from infection, or at most suffer only from a simple tertian fever; while those who harvest the grain, and especially those who thrash it and engage in other of the autumnal works, pay a heavy tribute to malaria. Besides agricultural labourers, those also are subject to malaria who are obliged to work at ditching, excavating, and other tasks - e.g., railroad construction, the building of fortifications, the diking of rivers, and so forth. The disease also takes hold of those who pass days and nights in malarious regions - e.g., brick-makers sleeping or staying in kilns, soldiers, carters, hunters, and tramps.

AGE.

Except in so far as the very young and the very old are less likely to be exposed to the infection, age appears to have no predisposition to the disease.

SEX.

The predisposing effect of sex is also nil in itself, though men are apt to be more exposed to the disease than women, excpet in certain localities where the contrary obtains.

RACE.

There appears to be a relative insisceptibility to malaria in many infected localities amongst the natives. This appears to be especially true as regards the negroes, Indians, Tamils, and the Arabs. The degree of this insusceptibility varies, however, in different localities and according to different observers. That the susceptibility of the negro is only about one third that of the white is general opinion in tropical countries.

DIET.

Residents in malarious regions believe that the fever may be caused by imprudences in diet - such as the eating of much fruit, especially unripe fruit. Although this is not strictly true, we can readily understand how the organism may be rendered less resistant to the action of the parasite is any indiscretion in diet is followed by gastro-intestinal disturbances, especially by a debilitating diarrhoea. When circulatory changes caused by digestive disorders already exist, perhaps also the localisation of the parasites in the capillaries of the gastro-intestinal mucous membrane,

as occurs in choleraic pernicious fever,may take place more readily.The susceptibility of the organism to the development of the specific poison is intensified by all such debeilitating factors as excessive toil,especially in the sun,mental disturbances,and insufficient food.

TRAUMATISM.

It has often been asserted that,where a previous attack of malaria has existed,injuries of various sorts are particularly likely to be followed by a relapse of the disease.It is often said,for instance, that an injury to the spleen,in a patient who has formerly had malarial fever,may call forth a ralapse. With regard to the effects of traumatism,the observations made on thousands of cases have not given any positive answer,while the complications of malaria with aother acute diseases have been,perhaps,rather surprisingly infrequent.It seems reasonable that trauma or operation,by reducing the vitality of the patient, should render him more susceptible to a fresh malarial infection,or more liable to a recrudescnec of an already existing process.In many hospitals,however,in malarious districts not a single case of post-operative malaria has,during the course of many years,been observed;so that the hypothesis of many of the chills occurring under these circumstances,generally supposed to be malarial,being in all probability septic is a reasonable one.

IMMUNITY.

It is a well-known fact that many persons are immune from malaria and experimental malaria,and the same is true of certain races,- at least,the latter present a varying degree of resistance to the infection.Thus,negroes inhabiting malarious regions in the tropics are less subject than white men in the same places to the grave forms of malaria,and,having once been infected,they are said to acquire a relative immunity more readily than whites.All observers,however, do not subscribe to this theory of racial immunity. Some attribute to the blacks an almost complete immunity,but this,as recent observations have demonstrated, is an error:possibly the various races of coloured persons differ amongst themselves in this respect. According to Plehn,the natives of the Kamerun coast seldom have fever,and when they do,the febrile paroxysms never last more than a few hours;they rarely ask the Europeans for quinine,and usually recover spontaneously in a few days.But a change of residence deprives them of this relative immunity,at least temporarily. The Malays and the Javanese,- according to Martin, whose observations were made in Sumatra,- enjoy a certain degree of immunity,suffering for the most part from mild forms only of the disease;and the Tamils are still less predisposed to malaria,although they are chiefly workers in the fields.Among the inhabitants of different regions,however,even in the same race there is often observed a varying power of resistance.For instance,it is known that in Italy the peasants of Venetia and of the Marches suffer terribly from malaria when they come to work in the Roman Campagna,while the

inhabitants of,it is said,Abbrùzzo and of the mountainous parts of Latium possess in general a greater power of resistance.The latter has been attributed to a natural selection effected by malaria upon the population,the custom of descending from their native mountains,during the season of agriculatural labour,into the salubrious plains having been observed by the inhabitants of these regions for centuries.Evidences of great variability in individual resistance to infection,and even examples of veritable immunity,are to be found among the fixed population of malarious regions.We have to distinguish a congenital immunity,which may be a family peculiarity,and an acquired immunity,which in the great majority of cases is not complete but only relative.Before asserting the complete immunity of any given individual,howeber,we must be sure that he has lived a sufficiently long time in a place where grave malaria prevails.Indeed,we may sometimes see individuals,who have been for a year or even longer in malarious regions without contracting the disease,suddenly fall victims to a grave infection when they had come to regard themselves as perfectly secure.It is necessary also to be certain that the person in question has actually been inoculated with the malarial germ.Indeed, for a long time there have escaped infection some who have always carefully avoided sleeping out of doors or with open windows,who have always slept under a mosquito bar,who,in a word,perhaps unconsciously have always so conducted themselves so as to avoid being stung by malarial mosquitos.In the case of white persons it is very seldom that we come across any instance of congenital immunity:yet they are to be found in all malarious districts if sought for.Many appear never to have had the disease and exhibit no splenic enlargement.The descendants may have bequeathed to them this immunity; and many such cases are on record.Acquired immunity is, however,much more common.It is often that one observes individuals who suffered from malaria,during the first year of their sojourn in the infected region,for many months,- usually from the summer or the autumn to the spring of the following year,but after that remained well,- having a fairly healthy appearance,and being capable of considerable work;but on examination they are found to be suffering from enlargement of the spleen, often of considerable size.There are also persons who, during a residence of many years,even fifteen or twenty, in a markedly malarious region,have never suffered from attacks of typical malarial fever,but are troubled from time to time with a slight feverishness which they attribute to an imprudence of some sort,but which is probably a very mild malarial attack excited by overwork or exposure.These individuals look fairly well, and they preserve their strength and ability to work often to an advanced age,but examination shows enlargement of the spleen.In the first of these cases there is a more or less complete acquired immunity following a series of febrile attacks;in the secind the individual is endowed from the first with a marked power of resistance,in consequence of which the infection has never run an acute or grave course,such as it usually does

in new arrivals in malarious places,but has rather been chronic from the beginning,and during this time the subject has been gradually increasing his initial resisting-powers until he finally acquires quite a notable degree of immunity.It should be stated,however,that examples of this sort are to be seen among the permanent inhabitants of malarious regions only in the class of overseers,stewards,and agents - those,namely,who are well-fed,relatively well-housed,and are not obliged to work,but usually pass the day on horseback directing the labourers and superintending the work.It is only under the most favourable conditions that acquired immunity can be developed in an ordinary labourer: certainly it is very seldom seen in persons of that class.Though in the above-mentioned rare cases there is established a relative immunity of great practical value,in the vast majority of instances the organism acquires gradually a certain degree of resistance to the infecting agent;but this resisting-power is not sufficiently strong to prevent relapses from time to time which finally induce a cachectic condition.Although,at first thought,the application of the term acquired immunity to cases of this sort,in which the individual is reduced to such an unenviable condition,does not seem justifiable,yet we find many proofs that such subjects are really more resistant to the action of the malarial germ than new arrivals who have never had the fever. For example,it is seen that pernicious attacks are almost always primary,or at least occur with the first relapses;it is common to find the spleen very soft,and but slightly enlarged,at the autopsy of one who has died of a pernicious fever,and,on the other hand, it is rare to find the characteristic parasitic condition of pernicious infection in an individual with a pronounced chronic enlargement of the spleen.It is perhaps correct to say that the majority of those who become cachectic,after a long sojourn in a malarial region,do not die of malaria,but of its consequences,and generally of complications - such as pneumonia and the like.At the autopsy of such a cachectic subject who has remained up to the end of his life in a malarious district,a recent malarial infection is excluded by the fact that the enlarged spleen is usually found of a bright red colour,and without a trace of melanosis.The study of the ordinary course of malaria,-both in those who leave the district after having acquired the fever,and in those who,remaining there,are continually subject to reinfection,- furnishes the proof that a relative immunity is gradually established during malarial infection.This fact is also to be observed in tertian and quartan fever; for,as we know,if the treatment is instituted properly at the beginning of the disease,we usually succeed in reducing it to a minimum,or even averting entirely the relapses;while in quartan fever the groups of attacks follow each other with the greatest obstinacy,separated by longer or shorter intervals of apyrexia,and,even when the patient is living amidst circumstances of the most favourable kind,the infection in some cases dies out only after many years of existence.The ingestion of quinine might be supposed to be the direct cause of

this.Indeed,most patients succeed in overcoming the fever,after a certain number of attacks,with that drug; then,after a certain period of apyrexia,the relapse occurs,the mildness of which,compared with the primary attack,might be thought to be due solely to the fact that the infection has been attenuated by means of the remedy.It may,however,be affirmed with certainty that this course is owing not only to the treatment adopted, but in great part to the modifications occurring in the human organism during the existence of the infection. Indeed,if we refrain from giving quinine to patients not suffering from a grave form of the disease,we find that,after a certain number of febrile paroxysms,the upward temperature curves tend to become less marked,and a spontaneous recovery takes place.But this cure is temporary only,and after a variable interval the fever returns,usually in milder form.Again,not only is the fever less prohounced,but all the effects upon the organism of the malarial poison manifest themselves in the successive relapses in continually lessening degree. For example,we find that patients,under equal conditions as regards the quantity of infection,become less anaemic in the relapses than in the primary attack.It is probable that the subjects of malaria were cured before the discovery of the properties of the conchona bark in this way.There can be no doubt that the spontaneous cure of the disease is primarily connected with the modifications which the infection itself produces in the human organism.Indeed,we cannot explain it at all unless we admit either a progressive attenuation of the parasites until they have lost gradually their pathogenic action and their capacity for multiplication,or a progressive increase in the patient's power of resistance to the pathogenic action of the parasites:in other words,an acquired immunity.While not denying absolutely the pathogenic action of the parasites may be weakened in the course of time,we yet cannot attach very great importance to their attenuation.Indeed,patients with chronic malaria,even when they remain permanently in a malarious region,where they are continually subject to reinfection with fresh virulent material,do not,as a rule,suffer from the grave forms of malaria as do the new arrivals.Furthermore,experiments have demonstrated that,when blood,containing very few parasites taken from a person who has spontaneously recovered from an attack of malaria,is injected into a healthy person,a grave form of infection may be induced in the latter.It is therefore the organism of the patient himself which prevents the parasites from developing their pathogenic action,and not the parasites which have lost of themselves their power of exciting the disease.We are forced to the conclusion that the defensive capacity of the organism has been weakened by the action of cold when a patient,- say,one suffering from a quartan fever,in whose blood the parasites regularly pass through their life cycle without inducing pyrexia,- is seized anew with febrile paroxysms,in consequence of the action of some occasional cause,such as a cold bath.It is very evident,then,that certain changes take place in the patient during the febrile attacks,by means of which

he acquires an immunity from the effects of the specific cause of the disease.But this immunity,as is the case also in certain other infectious diseases,is of brief duration,and when it is weakened the relapse occurs;this confers anew upon the patient an increase of his period of apyrexia.The fact that even reinfection does not,as a rule,take on a grave course,and that there is a diminishing intensity of the successive seizures,can be referred to the persistence of a part of the acquired immunity after every apyretic period. The usual course of the malarial infection can probably be explained in this way.The results of the researches made up to the present time do not allow of the analysis of this acquired immunity of malarial subjects in the same manner as has been done in the case of some other infectious diseases.Attempts to confer immunity upon man artificially have hitherto failed;but we must remember that the experimental study of this question in the human subject is attended with great difficulty. It is evident that the practical value of this relative immunity acquired by malarial subjects is very small, even after a long course of the infection;for,if we except the small number of persons who become immune after a few months of fever to such a degree that they can remain in the malarious region without suffering from further attacks,most subjects acquire this relative immunity at the cost of a chronic infection or cachectic condition.This causes a progressive degeneration of the races living in regions of intense malarial prevalence,and hinders the natural selection through the action of which we might,a priori,look for the creation of an immune race.The fact that the agricultural population of malarious regions is constantly being thinned out and must be constantly recruited by labourers coming from non-malarious districts,and also that the above-mentioned delection in the case of the white races does not act in such a way as to produce practically useful results,has been demonstrated by very long experience.It is a matter of doubt whether a certain degree of immunity from malaria is conferred by other affections.It has been widely believed that some skin diseases afford protection against the fever. This is asserted by many in the tropics,especially in the case of lichen tropicus and tropical furunculosis - infections due,it is alleged,to the staphylococcus pyogenes aureus.The same opinion is held in India.But, admitting the the correctness of this observation,we may yet ask whether we have to do here with a true immunity conferred by the cutaneous affection,or whether these patients escape malaria because,owing to the condition of their skin,inoculation by the malarial germs is impossible.It is probable that,if the infected mosquitos do puncture the skin,the conditions essential to their development are not existing for the malarial sporozoites in the blood-vessels of the infiltrated and inflamed dermic area;for it is said that those subjects are exempt from malaria only so long as the disease of the skin lasts.

MANNER OF INFECTION.

The nature of the infective agent in malaria has been demonstrated by the researches of Laveran and others, while its specific action has been abundantly shown by clinical observation and inoculation experiments.Three

modes of infection have been suggested - viz.,directly from the external world,subcutaneous or intravensous inoculation of human blood containing the parasites, and by passing through the placenta of a malarious mother to the circulation of the foetus.These it is necessary to consider at some length.

(1) That the natural way of contracting malaria is by inoculation is obvious from what we have said regarding the life cycle of the malarial parasites in certain species of mosquitos.If it is admitted that the facts above-mentioned concerning the life cycle of the malarial parasites in the Anopheles represent practically the entire biology of these beings outside of man,then we may assert positively there can be no other.The conclusion that man acquires malarial fevers solely through the bites of certain species of gnats,by means of which occurs inoculation of the malarial sporozoites, would be the logical and necessary consequence of such a promise.This conclusion,which is founded upon a series of facts tending to exclude the possibility that the infection may take place in other ways,can be maintained,in spite of the fact that we cannot positively deny at the present time that the malarial parasites may exist under other forms than those now known to us. Independently of what we know regarding the biology of the parasites within the bodies of the diptera,this renders the study of the problem as to how fevers are are contracted necessary;that is to say,it is necessary to see what clinical and epidemiological experience in malarious regions teaches,and then to set forth in detail the experiments upon which the theory of inoculation is based.Such an exposition is the more necessary since,even at the present time,many authors,while recognising the importance of mosquitos as vehicles for the transportation of the malarial organism,yet refuse to admit that inoculation is the sole mode of infection, and incline to the belief that,as Lancisi held,there are multiple channels of ingress of the malarial germs. This opinion is now,however,being rapidly abandoned. There were three theories for long entertained as to the mechanism of infection by the malarial germs - viz., the water theory,the air theory,and the inoculation theory.The latter,that the malarial germs are inoculated into man through the agency of misquitos,is the only one which has up to the present time been demonstrated experimentally.Now,regarding the water theory,the hypothesis that man may become infected with malaria by drinking-water from marshy places is supported by many facts adduced by its advocates.Thus,it has been often affirmed that of certain individuals living in a special locality under otherwise identical conditions, but drinking water from different sources,some were attacked in large proportion by malaria,while others were spared by the disease.In certain insalubrious localities it has sufficed to provide a pure water-supply to the inhabitants,water from stagnant pools having previously been used for drinking purposes,to cause the malarial fevers to disappear.Examples have been cited of travellers who,while passing through malarial countries,had succeeded in preserving themselves from the fever by drinking only boiled water,

while large numbers were attacked who did not take this precaution.In very healthy places the fever might be contracted when water brought from an unhealthy place was used for drinking,and those individuals who were most apt to take the fever were the ones who had consumed the greatest amount of the suspected water.That many of the facts upon which their arguments are based are not above criticism is now recognised by many advocates of this theory advanced by Laveran. Indeed,many of the facts themselves are not definitely established,and are rather vaguely stated.In many cases no proof is given that the fevers which followed the ingestion of the alleged unhealthy water were truly malarial.Others of the facts given are open to various interpretations. For example,when it is affirmed that the intensity of the malaria diminished after a district had been supplied with pure water,we must remember that this effect may have been due to a general improvement in sanitation;malaria,we know,retires before the progress of hygiene and civilisation.When we hear of individuals living under identical conditions,of whom those acquired malaria in the greatest number who were forced to drink water from stagnant pools,we forget that this very fact otself shows that the conditions were not really identical.We cannot exclude the possibility that those who drank the stagnant water may have been exposed more than others to the occasional causes of malaria,or offered less resistance to the germs of the disease.Furthermore,the possibility that the drinking of stagnant water may facilitate the development of the parasites which have already,- as we know happens through the influence of poor food,chilling of the surface,and debilitating conditions,- cannot be excluded.The results of experience in such places as the Roman Campagna may be opposed to these facts.Many lacalities,indeed,are known in the environs of Rome which are exceedingly malarious,yet in which the inhabitants drink the same excellent waters as those supplied to the city itself.In other places,Ostia for example, good drinking-water has been introduced with no improvement in respect of malaria.In various other parts the study of epidemics of the disease leads to the inevitable conclusion that water is of no importance as a vehicle of infection.Experiments,with a view to ascertaining whether water taken from malarious to absolutely healthy districts could convey infection to healthy individuals drinking it,have been carefully carried out in various regions.Celli,for example,had healthy persons in the Santo Spirito Hospital drink water for several days which had been collected in the Pontine marshes and from stagnant pools in the suburbs and environs of Rome,but with negative results.Negative results have also been obtained from other experiments. The question has been studied in India by Roos,who adduces a single fact in favour of the water-borne theory of the disease.Led by the hypothesis previously mentioned,-according to which the mosquitos,having taken in human blood charged with malarial parasites, go to deposit their eggs in water and there die,whence the infection of the water itself,- he had a person

drink water in which there were dead mosquitos containing malarial parasites.Eleven days later,the subject of the experiment had an attack of fever which lasted three three days and ceased spontaneously,no relapse following.In the blood of the patient,Ross declared that he found many annular forms of the plasmodium.But,in other individuals in whom he repeated the experiment,there followed no fever which could be certainly called malaria.This renders the valuemof the first nil;and no one has yet been able to propagate the disease by the ingestion of water from swampy malarial places.At one time both profession and laity believed in the air theory;and the advocates of it maintained that the free life of the parasite is passed in the soil or in the water of marshy places,whence it passes into the air and infects man through the channel of the respiratory organs.Numerous researches have been made with the aim of discovering the germs in the so-called malarial materials,but all without result.Among the most recent of these experiments we find those of Grassi and Calandruccio,who held,some years ago,as a definite fact, that the malarial parasites were rhizopods or forms repated to them;they therefore sought for them among the members of this group which are found,in their free existence,in the so-called malarial materials - such as uncultivated fields,made land,rice,fields,and so forth. They vaunted the theory that the malarial parasites were to be found in the genus Amoeba,in its wide sense; and they assumed that certain amoebae,living in a non-parasitic condition,became encysted,were carried into the air,and so entered the body of man,there developing and taking on characters somewhat different from those of their ancestors in the non-parasitic life.In support of the air-borne theory,however,it cannot be cited,and for the reason that this assumption is overthrown by the results of modern researches.Various observers have found considerable difficulty in explaining by the air-borne theory certain of the best attested epidemiological data of malaria.It does not,in fact, satisfactorily explain how the germs enter the air from the soil,to which latter epidemiologists in general assign the origin of the miasm;nor does it expalin why at different hours of the day there is such a variation in the charge of malaria in the atmosphere;nor,again, does it expalin why the disease is not carried by winds, or at least is not notably so carried.To the theory that the germs could rise into the air from the soil along with the dust we may object that malaria does not act like a disease caused by the inhalation of dust;and, furthermore,that the days of greatest danger are windless,when less dust rises,and especially on the still warm days following a rain in which no dust rises from the damp earth.If it were alleged,on the other hand, that the germs pass into the air from humid soil,then it would be necessary to assume,- this supposition being altogether arbitrary,- that something occurs with great faciltiy,and,as a rule,in the case of malarial germs which,in that of ordinary bacteria,has never been satisfactorily shown to take place.Hirsch,Tommasi-crudeli,and other have asserted that the wind transports malaria only very short distances,if at all,and that

practically it plays no part in the diffusion of the disease.If the emanations from the Pontine marshes were the cause of the malarial fevers in the Roman Campagna,as Lancisi believed,then it is impossible to understand why the cities of Velletri,Genzano,Ariccia, Albano,etc.,which lie between Rome and the marshes,and ought to receive first and in greater concentration the noxious emanations transported by the wind,should be entirely free from malaria.If the latter could be transported to a considerable distance by the winds,we cannot understand its presence in strictly circumscribed regions in various parts of the world.It is also worth mentioning that that Tommasi-Crudeli called attention to the well-known fact that malaria rises but a short distance above the ground.Experience has taught the inhabitants of the Pontine marshes to sleep at night, during the fever season,on platforms raised,from thirteen to sixteen feet,on poles.Our author also says that the fact that the germs do not rise far above the plain will explain the notable differences that exist in regard to malaria between Norma,Sermoneta,and Sezze - cities lying above the Pontine marshes.The sea breeze which blows in summer in Rome does not bring danger, yet it passes over all the swamps on the coast.But it is not,says Tommasi-Crudeli,that this breeze does not carry malaria in the direction of Rome,for it does carry it and in large amount;but it carries it while acting at the same time as a ventilator - that is to say,it scatters the germs in every direction,although it is a current of air of very slight velocity.Nevertheless,it is not easy to believe that a current of air,carrying every day,as he believes,a large quantity of malarial germs,does not fill the city with malaria; and it is a proper conclusion that it does not carry the germs of the disease at all,and that his argument is based on a false assumption.In short,the air-borne theory of malaria does not permit of a satisfactory explanation by epidemiological data;and,despite the most ingenious attempts at an explanation,it is scarecly possoble to conceive how the winds do not transport the germs of malaria of these are present in the air. On this theory it is impossible to explain the great differences as regards the danger of infection between waking and sleeping in a malarious region;and also the fact,which has been repeatedly observed,that the crews of ships lying,off the most insalubrious coasts,escape - only those men being attacked whose duties compel them to pass a large part of the time on shore.The insurmountable difficulties encountered in accepting the air-borne or the water-borne theories naturally lead us to think of some other mechanism by which the malarial germs may gain entrance to the human body,and more especially of inoculation.We are driven to this hypothesis partly by the exclusion of the two preceding ones;partly by the fact that subcutaneous or intravenous injection of malarial blood is the only means by which hitherto malarial fever has been produced experimentally;and partly by the analogy of human malaria,in a parasitological sense,to Texas fever - this being due to inoculation by a kind of tick.The probability of

this theory was demonstrated by Bignami in 1896 - he at the same time affirming that it readily and satisfactorily explains many facts that are difficult of explanation by the air-borne theory. Thus, admitting that malaria in mankind is the result of inoculation by mosquitos, it is not difficult to explain why it is practically not carried by the wind; it is also easy to understand why the danger of acquiring malaria is greatest in the evening and the night. We see at once why the infection does not rise far above the ground. We comprehend readily the danger of sleeping in malarious districts; and, finally, this theory explains perfectly the well-known prophylactic efficacy of mosquito-nets in regions where malaria prevails. It likewise expalins the efficacy of the prophylactic measures adopted, as the result of experience, by the inhabitants of malarious regions; many of the precautions taken against the fever seem really to be taken against the attacks of the insects in question. All this, indeed, accords exactly with what we know of the habits of mosquitos in malarious countries, which sting especially at night and during the evening, do not fly far from marshy places where the proper conditions of their existence prevail, are in hiding during the day out of the way of the winds, are most numerous in places where malaria prevails, disappear from places where sanitary measures have removed the conditions necessary to their existence, and do not fly to any great height above the ground. Bignami was led by these facts to the conclusion that malaria acts like a disease inoculated through the stings of mosquitos. In order to verify this hypothesis experimentally, it was necessary to cause healthy men, living in a positively non-malarious district, to be bitten by mosquitos transported from a place where malaria prevailed. After some fruitless attempts, these experiments have given positive results - the precaution being taken to capture adult mosquitos in a pronouncedly malarious region somewhat late in the season, as the number of infected insects is much greater at that time than at the beginning of the season of malarial prevalence. The first experiment, attended with absolutely positive results, was carried out in the person of one Abele Sola, an inmate of the Santo Spirito Hospital for the past six years, who suffered from a nervous affection but had never had malaria. He offered himself voluntarily as a subject of the investigation. This was carried out by liberating, in a suitable room provided with mosquito-bars, mosquitos brought from Maccarese, a marshy place famous for the intensity of its fevers. It is not necessary to describe these experiments in detail, as they are to be found in Bignami's work. It is sufficient for our purpose to observe that with these three new cases of malaria experimentally produced by the Anopheles alone, the inoculation theory acquires a very strong confirmation. The individuals submitted to experiment have been few in number; but it is to be noted that, whenever an attempt was made under appropriate condition to excite the fever by inoculation, it was successful. The experiments have shown that very few punctures by very few infected mosquitos suffice to give the fever; a postive result has been obtained with only two

infected insects,and it is quite certain that one alone would be quite sufficient.When we think of the enormous number of malarial sporozoites which can be found in the cells of even one tubule of a salivary gland of Anopheles, this fact need cause no astonishment.This answers the objection advanced by many that there are malarious regions in which very few mosquitos are found;the number of the infected insects,and also their species,must be taken into account.It appears certain that a solitary specimen of Anopheles may infect several persons.Indeed, there have been found sporozoites in the middle intestine in mosquitos which had bitten healthy individuals,and caused in them an attack of malaria.In this case,therefore,even had the Anopheles emptied the entire contents of the salivary gland at each bite,the insect would be capable of inoculating other persons with the fever,as the glands would again be invaded by other sporozoites from the middle intestine.Finally,we may take it as proved that the only way in which man takes malarial fever is by inoculation effected by certain species of mosquitos.

(2) Some of the older writers believed that malaria could be transmitted in the sweat,but this opinion we now know to be erroneous.Mannaberg says that Dochman considered that he had reproduced a malarial fever by inoculation with the contents of an herpetic vesicle occurring on a sufferer from quartan fever;but this experiment has never been repeated,and the results lack confirmation.Inoculation with blood containing the malarial parasites will,however,transmit the fever to a healthy individual.This fact has been experimentally demonstrated by Gerhardt,who saw a typical intermittent fever reproduced in an inoculated subject;and it has been corroborated by Marchiafava and Celli,and others who, by finding in the blood of the inoculated person the same parasites which were present in the blood of the patient from whom the material for inoculation was derived,leave the question no longer in doubt.Innumerable other investigators have done the same thing;and in this way has been forthcoming a confirmation of the doctrine of the multiplicity of species of malarial parasites.Furthermore,they gave results which were of great utility in the study of the doctrine of incubation.The transmission of the disease occurs equally whether the blood is taken during the apyretic period or during a febrile paroxysm,whether it contains young parasites or those in process of development,or whether it contains sporulating forms.In view of what we know regarding the biological significance of the crescent forms,it is not surprising to learn that the latter, when injected alone,do not transmit the disease.A subcutaneous injection alone is necessary to convey the infection to an inoculated subject;it is not necessary to inject the malarial blood into the vein of the recipient,as has been done in most of the experiments. It is not even necessary to inject several cubic centimetres,as was done especially in the earlier researches; a fraction of a cubic centimetre will suffice,and even less than one drop will do.Most of the experiments were made by injecting blood in the natural state,soon after

it had been drawn from the patient's vein;but positive results have also been obtained with the injection of defibrinated blood,and of blood obtained with leeches, as well as of blood separated by centrifugation.In one case Di Mattei collected the blood from a case of epistaxis occurring in a malarial subject,in a test-tube containing sterilised and distilled water,at a temperature of 98.6°F.,and injected a drachm of this mixture of equal parts of blood and distilled water;the subject inoculated had a fever fourteen days later.If,however, malarial blood is mixed with an equal quantity of distilled water,the mixture being well shaken,a healthy man may be inoculated with the product,after it has been allowed to stand for an hour,with impunity.If blood rich in parasites is dried at the temperature of the air,and then dissolved in a tepid physiological salt solution, an injection of the solution will be innocuous,even when the blood has been left in the dry state for a very short time.It has been noted that blood also,which is filled with parasites,taken from a patient with pernicious fever may be injected without results,after the administration of large doses of quinine,even though no morphological changes may be observed in connection with the parasites at the very moment of injection.It is only from man to man that it is possible to have a transmission of the infection through the injection of malarious blood;and then it is extremely rare for the inoculated person not to take the fever,a positive result being the almost constant rule.On the other hand,all attempts to induce malaria in various species of animals, by injections of blood containing the parasites of human malaria,have been uniformly unsuccessful,even when the subjects of the experiments were animals which are subject to infection with haematozoa very much resembling those found in man.Various experiments, always negative in their results,have been made on various species of monkeys Di Mattei (a macaco),Angelini (a cynocephalus sphynx),Richard,Fischer,and others. While positive results of the injection of malarial blood from man to man are almost constant,it is singular to find that contradictory results have been noted in experimental attempts to transmit the disease from one bird to another,even of the same species and variety. Grassi and Feletti,and Di Mattei have always had negative results,though Celli and Sanfelice claim to have seen the disease transmitted in this way in certain cases.In the"Zeitschrift für Hygiene" (xxxii.,1899) R. Koch says that it appears tjat,according to the researches of Pfeiffer,the halteridium of not transmitted from bird by means of infected blood,whereas the proteosoma is thus conveyed with great facility.The apparent contradiction may thus be explained.

(3) The question as to the passage of the malarial germs through the placenta has often been discussed, many authors affirming that such does actually occur - although there has never yet been reported any well studied cases which demonstrated,in a way to silence all objection,the possibility of the infection of a foetus in the mother's womb.Most investigators,although having at their disposal a great amount of material for

study, have never seen a child with malarial fever immediately after birth, nor have they succeeded in finding the parasites in a foetus removed from the uterus of a woman dead of pernicious fever in whose blood was an enormous number of germs, or in one born as a result of abortion occurring shortly before the mother's death. Numerous examples of this are to be found in the literature; and the same, while naturally they do not exclude the possibility of the passage of malarial parasites through the placenta, demonstrate, nevertheless, that even if such a thing as a congenital malarial infection exists, it is at least exceedingly rare and exceptional. In order to explain this absence of malarial parasites im the blood of the foetus, - which is certainly the rule, - the fact has been invoked that the malarial parasites show no tendency to wander out of the blood-vessels. Even in the case of small capillary haemorrhages, which are sometimes very numerous in the brain in comatose pernicious fever, no parasites are found in the extravasated red blood-corpuscles, although they are present in great numbers in the blood within the vessels in the neighbourhood; the red corpuscles in the blood exudate in malarial pneumonia also contain no parasites. All these facts make it appear very improbable that the parasites can pass from the maternal to the foetal circulation during their intraglobular existence. If, however, it were held that this passage is possible during the brief period in which the very young parasites are living free in the blood plasma, in order to explain the negative results above-mentioned we should have to assume that the foetal blood is not adapted to the development of the parasites. The fact that the plasmodia do not invade the nucleated red corpuscles, and most probably not the young red globules, has been adduced in support of this theory. Some authors claim to have absolutely demonstrated the passage of the malarial germs from the mother to the foetus. Thus, Laveran cites two observations - one of Bouzian and the other of Bein - which, he asserts, prove beyond doubt the existence of congenital malaria. The original report of the first of these cases has not yet been published; but Bein's cases is not above criticism since the presence of malarial germs in the child's blood was noted too long after birth, and the possibility of post-natal infection could not be definitely excluded. Mannaberg cites, as positively conclusive, a case published by Ducheck in 1858. The case was one in which the mother of the child had suffered from intermittent fever during her pregnancy, and who died three hours after being born. At the autopsy there was found a notabale enlargement of the liver and spleen, together with much black pigment in the form of irregular lumps and granules in the spleen and in the blood of the portal vein. There has been no publication of the original report of this curious case; so that we may take it that no truly demonstrative case of congenital infection has been recorded in the literature since the discovery of the malarial parasites. Furthermore, the splenic enlargement may have been due to some non-malarial cause - e.g., syphilis.

PATHOLOGY.

It is mainly by the study of cases of pernicious aestivo-autumnal fever that our knowledge of the anatomical alterations in the internal organs has been derived, for cases of regular intermittent fevers are so rarely met with upon the post-mortem table. The pathology of malarial fever has been vastly expanded by the discovery of the parasite of the disease by the observers already mentioned. One of the most interesting points which at once strikes the careful observer is the extreme distribution of the malarial parasites within the body, and the anatomical changes produced by them in different cases. The symptoms observed during life may be directly influenced by the localisation of the germ of the disease. The melanosis, which gives a characteristic colour to many of the organs, is the most striking point in the appearance of the viscera in cases of malarial fever. The degree of their affection varies in different cases; and the pigmentation in question is due to the accumulation of the pigment produced by the parasites from the haemoglobin of the blood-corpuscles. Its distribution, as in the case of the parasites, also admits of considerable variation.

BRAIN.

Cases of comatose pernicious fever furnish the most striking anatomical alterations in the brain. That organ may be the seat of few macroscopical changes. Melanosis may be entirely absent. At times, however, there may be a slight subpial oedema with hyperaemia of the cerebral substance, and perhaps punctate haemorrhages; more commonly, however, the gray cortex shows a gray or slaty or chocolate colour, which may be quite deep. The vessels are markedly injected, and in places, punctate haemorrhages may be found. In these instances the microscopical changes are most remarkable. The cerebral capillaries are crowded with parasites, which are, for the most part, within red corpuscles, and may form an actual complete injection of many of the cerebral vessels. This is generally most striking in the gray substance. These parasites, - usually of the aestivo-autumnal type, - may be in all stages of development, though generally one of the stages is most marked. Sometimes, in cases where death has occurred during the paroxysm, actual thrombi of segmenting organisms may exist. Sometimes the organisms may not be so numerous, but evidence of their previous existence is found in free clumps of pigment and swollen pigmented endothelial cells, as well as leucocytes containing pigment and red blood-corpuscles. There is usually decided granular and fatty degeneration, and often pigmentation of the endothelium of the vessels - a change upon which the punctate haemorrhages probably depend. Some endothelial cells may be greatly swollen, almost occluding the lumen of the vessels: these, as has been demonstrated, especially by Monti, may contain a considerable number of well preserved parasites in various stages of development; they may be within shrunken

or brassy corpuscles, or full grown and free. Occasionally large macrophages are seen almost occluding the capillary; these are, in the opinion of Monti, endothelial cells which have broken up and circulate free in the blood-stream. These anatomical alterations are best seen in the comatose form of pernicious malaria. In some instances different parts of the central nervous system may be differently affected. In one cases, for instance, studied by Marchiafava (Lav. del. III. Congr. del Soc. Ital. di Med. Int., Roma, 1890, 142), where the patient died of symptoms of bulbar paralysis, a special localisation of the changes was noted in the medulla. In other instances the cerebral lesions may be slight; one is unable to discover the collections of parasites in the capillaries, and well as the degenerative changes in the endothelium thereof. There have been interesting results derived by Monti (Bull. d. Soc. Med.-Chir. di Pavia, 1895) during the course of his researches regarding the nerve cells in the gray cortex in pernicious malaria, using Golgi's method. In some cases the elements were, so far as could be made out, quite normal, while in others interesting changes were noted: these cases were chiefly those showing grave nervous symptoms, such as coma, during life. Usually cells more or less profoundly altered were found among other cells and fibres which were quite normal, although a tendency to a focal arrangement of these changes could be made out. The alterations affected chiefly the protoplasmic prolongations of the nervous cells of the cerebral cortex. Sometimes the prolongations app--eared thinned and stuffed with fine nodes. Not infrequently these alterations were limited to the more delicate and distant branches, though it was not difficult to find cells of which all the dentrites presented the beaded appearance which is so well presented by the nerve cells of animals ded of inanition. In other points the alterations consisted of simple irregularities of contour in dentrites which were much thinned, extending from cells the bodies of which were sometimes normal, more often swollen, rarely thinned, shrunken, or atrophic. Coarser alterations were, however, not wanting. Cells were found whose dentrites showed coarse varicosities and very marked constrictions, so that they appeared as if formed of protoplasmic matter connected only by the finest filaments of protoplasm. In the case of animals whose brians were made the seat of embolism by the injection of lycopodium, similar changes were observed. The axis cylinders were, in most of Monti's cases, well preserved; the principal lesion appeared to consist in alterations of the protoplasmic prolongations. In some cases, however, especially in one severe cases of comatose pernicious fever, certain alterations were made out in the axones. In this case the alterations in the nervous elements appeared more marked throughout the brain than in other cases; the alterations in the dentrites were more frequent and marked, while the nervous prolongations also, had, in many points, lost their normal character. Our author believes that these changes are due to the grave circulatory disturbance, - many of these alterations are not dissimilar to those described in animals after the injection of ricin by Berkley, - the occulsion of capillaries, lesions of their walls, the stasis, and the haemorrhages produced by the malarial parasites.

SPLEEN.

The changes in this organ in malarial cases are very characteristic.It is always enlarged;and what has been termed the acute splenic tumour is pronounced.The capsule is tense.The parenchyma is cyanotic,and sometimes of a markedly slaty gray colour;it is soft and is often diffluent.In acute malaria death may often occur from rupture of an enlarged spleen.Microscopically,the pulp contains enormous numbers of red corpuscles,many of which contain parasites.These parasites may be in different stages of development.Generally the pigmented and segmenting forms may be found in large numbers;and sometimes,in the same organ,different areas show separate groups of parasites in different stages of development.Free forms of the parasite are relatively rare. One of the most striking appearances in the splenic pulp is,however,the presence of great numbers of phagocytes,some smaller and apparently leucocytic in nature, others very large cells,rich in protoplasm,containing a single large nucleus and occasionally a coarse granulation.These cells may reach an enormous size.They are laden with pigment,either in large clumps or spheres,in rodlets,or in very fine granules;the granules sometimes present the same arrangement which they had in the body of the parasite.The fine pigment may be distributed in delicate lines throughout the whole mass of protoplasm of the phagocyte;it often seems to vary in colour in different parts of the cell;but,on focussing,this appearance is found to be due to differences in plane. These large cells also contain red corpuscles,which are often partially or completely decolourised and contain parasites;and,finally,entire small phagocytes with their included pigment or corpuscles,as well as clumps of haemoglobin,of the colour of old brass,and fragments of degenerated red corpuscles.Golgi and Monti have called particular attention to the frequency with which these macrophages contain apparently well preserved parasites in different stages of development.They believe that the shrunken and brassy parasitiferous red corpuscles are engulfed in the phagocytes as would be any foreign body,while the included parasites continue their development within.Some of the macrophages may show evidences of necrosis.In some cases one may find in the pulp actual focal necroses,very much like those seen in enteric fever.In the intercellular spaces in the pulp one may find free malarial pigment.Pigmented polymorphonuclear cells are relatively rare;the small mononuclear elements and the lymphocytes of the follicles never contain pigment.The capillaries are usually filled with corpuscles containing parasites,while the splenic veins ¾ though they always contain fragments of blood-corpuscles and phagocytes containing pigment - show relatively few.

LIVER.

The enormous number of parasites and the vast amount of pigment contained in its capillaries give to the liver very often an intense slaty gray colour.The distribution of the pigment is different,however,in this acute malarial infection from that characteristic of repeated attacks.There is always a marked cloudy

swelling.Microscopically,the capillaries are often clouded with leucocytes and contain numerous phagocytes; some of the largest macrophages are here observed.Not infrequently the endothelial cells may also be observed to show evidences of phagocytic action.The perivascular tissue in the portal spaces may show numerous pigment-bearing cells;while frequently liver cells may be found to contain clumps of pigment derived from the blood and altered red corpuscles.This condition,similar to that observed in pernicious anaemia,accounts,doubtless for the polycholia and the subicteric hue so commonly observed in the malarial fevers.In the intralobular veins macrophages are not infrequently observed;ordinarily, relatively few parasites within red corpuscles are found within the vessels:these are numerous in the interlobular branches of the vena portae.Amongst the hepatic changes that of great interest are occasionally occurring disseminated areas of local necrosis of the liver elements with fragmentation of the nuclei,wandering-in of the leucocytes,and sometimes with evidences of proliferation of cells in the surrounding tissue.These changes are very similar to those already noted in typhoid and other acute infectious diseases,and proven by Welch and Flexner (Johns Hopkins Hosp.Bull.,No.20, March,1892) to be produced in diphtheria,and by Reed (Johns Hopkins Hosp.Reps.,Vol.v.,1895) in typhoid fever, by a circulating toxic substance.The occurrence of these foci in the liver was first described by Guarnieri (Atti della R.Acadd.Med.di Roma,1887,S.2,v.,iii., 247-266),who ascribed them to the cutting-off of the nutrition by the extensive blocking of the intralobular capillaries with pigment-bearing phagocytes. In association with many of these areas Barker (Johns Hopkins Hosp.Reps.,Vol.v.,1895) describes and pictures capillary thromboses.

LUNGS.

The substance of the lungs may show evidences of necrosis;and the alveolar capillaries present,as a rule,large numbers of phagocytes,which are,however, smaller than the largest macrophages of the liver and spleen.Occasionally pigment may be found in the endothelial cells of the capillaries and small veins, but much more rarely than in the capillaries of the brain and of the liver.Leucocytes containing malarial pigment are seldom found in the interior of the alveoli.Mononuclear phagocytes are much more frequent than ordinary polymorphonuclear leucocytes,which,when present, contain,usually,finer,smaller particles of pigment. The macrophages are generally collected about the periphery of the smaller veins.The endoglobular parasites show,usually,all stages of development.The endothelium of the capillaries and small veins rarely contains pigment,in sharp contrast to the condition existing in the brain.It is a remarkable fact that the areas of broncho-pneumonia,which are not infrequently found, contain only the ordinary polymorphonuclear leucocytes and alveolar epithelial cells,pigmented elements being very rarely present.The capillaries of the septa may be filled,however,with pigment and macrophages.The diminished vitality of the pigment-bearing cells,- which have,to a certain extent,lost their motile power and are thus less able to pass through the vessels,- is considered by Bignami to account for this.

KIDNEYS.

The gross appearance of these organs differs but little from the normal, and the changes in them in acute malaria are usually much less marked than in the liver and spleen. Evidences of pigmentation are usually wanting on gross examination. The malarial parasites and phagocytes are usually present in smaller numbers, the quantity being disproportionately small in comparison to the alterations of the parenchyma which are sometimes to be found. The glomeruli, however, are ordinarily considerably pigmented, the pigment at times being seen within large white cells within the vessels, sometimes in the glomerular endothelium. Endoglobular parasites are rarely seen in the capillaries of the glomeruli; they are more common in the intertubular vessels, but are rare even there. Focal necroses of the epithelium, especially of the convoluted tubules, are at times some of the marked changes in the parenchyma. The most important lesions consist in exfoliation and degeneration of the epithelium lining the capsules. Albuminous exudates within the glomeruli were found by Bignami only in algid pernicious fever. Pellarin (Arch. de Méd. nav., 1865), Benoit (ibid.), Kiéner and Kelsch (Arch. de Phys., 1882) have well described the renal changes in cases of haemoglobinuric fever. The capsule of the gland is easily detached; its consistency is normal. The kidneys are somewhat increased in size, the colour varying from a deep reddish-brown to a light yellowish-brown coffee colour in more anaemic individuals. When the colour is pale, irregular pinhead points and blotches of a maroon colour are to be seen upon the surface, some as large as several millimetres in diameter or area. They are also scattered throughout the cortex. These have been described by Kelsch and Kiéner to be due to pigment deposits; they are not visible in more congested kidneys. The pyramids are of a deep-red colour from the intratubular haemorrhages. There are also peculiar changes to be seen under the microscope. The epithelium of the convoluted tubules and of the large branches of Henle's loops are very opaque, the nuclei being scarcely visible. This is due to an infiltration of the protoplasm with a diffuse colouring matter, and fine pigment granules which are rendered more evident by caustic potash. These granules are extremely small, and separately appear of a yellowish colour, while, en masse, they have a brown shade. The epithelial cells are swollen, and bulge into the lumen of the canal. Occasionally a cell shows a hyaline protusion, which seems on the point of escaping. In some tubes the epithelial covering is represented only by a thin protoplasmic layer with a homogeneous surface, appearing as if eroded down to the level of the nuclei. The lumen of the tubule is filled with clumps of amorphous material or casts mixed with this pigment to a greater or less extent. The brown specks and blotches seen macroscopically represent groups of tubules, the epithelium and lumina of which are crowded with similar masses of pigment; but pigment may also be found in larger granules - granules nearly as large as a red blood-corpuscle, and more or less spherical; they are refractive, of a colour varying from a yellow ochre to a deep brown, and are sometimes accumulated in epithelial cells which bulge so as almost to occlude the lumen. Sometimes they

occupy the lumen and form conglomerations, taking the form and shape of casts; sometimes they are fused into a vitreoid mass. Between the opaque dark casts formed by the fine brown granulations and the almost vitreoid casts composed of the large orange coloured granulations every intermediate stage may be seen in the same preparation. Generally this pigment gives no reaction for iron, though Kelsch and Kiéner have obtained this reaction from certain granules in one case. The finely granular substance is found, according to these authors, more particularly in cases where death has occurred in a pernicious paroxysm, while the larger forms of pigment are more frequent in cases of long duration. In the glomeruli, as well as in the blood, Kelsch and Kiéner have never seen the large varieties of the granules, though the finer granules are numerous. Between the glomerulus and the capsule, usually near the mouth of the tubule, there is often quite a collection of granules, which are also found sometimes in epithelial cells, sometimes free. In the glomerulus itself one may see fine granulations disseminated in its substance, and apparently included in the cells of the capillary walls. More rarely granulations may be accumulated in a capillary loop. In some cases there are small interstitial haemorrhages. The pyramids show few changes. The same varieties of casts as above noted may be found, and the same collections of pigment. The epithelium is usually intact though sometimes protuding and vesicular cells suggest that they may take part in the formation of hyaline material. Blood-corpuscles are almost invariably found to fill a number of the renal tubes.

SUPRARENAL CAPSULES.

Pronounced alterations may be found in connection with the adrenal glands. There are irregular areas of vascular dilatation, parasites being numerous in the distended vessels. Macrophages, with varying contents, may be present in considerable numbers. True adrenal cells may be found enclosing malarial pigment and infected corpuscles, and the endothelial cells of the vessels may be phagocytic.

GASTRO-INTESTINAL CANAL.

Beyond the presence of melanosis, there are few changes to be seen in the stomach and intestines under ordinary circumsrances. It is to be remembered, however, that the intestinal mucous membrane may be of a dark steel-gray colour in conditions other than malaria. In the majority of cases the gastro-intestinal mucous membrane is not particularly sought by the parasites, though the microscope may reveal a considerable number of them, especially of the full-grown and segmenting parasites, in the capillaries of the mucous membrane, together with numerous pigmented cells and apparently few pigment clumps. This region may be the seat of the main localisation of the affection in other instances, as pointed out by Marchiafava and Bignami. Cases of this sort are frequently associated with marked gastro-intestinal symptoms, some showing a clinical picture very similar to that of Asiatic cholera. Macroscopically, there may be intense hyperaemia with punctate haemorrhages in the gastro-intestinal mucosa; and there may be a distinct dusky slaty tinge as well. Here the capillaries throughout the gastro-intestinal tract may be crowded

and blocked with parasites, free and contained in the red corpuscles, or in phagocytes. As in the case of the brian, actual thromboses may exist with necrosis of the epithelial covering and ulceration.

BONE-MARROW.

Though often almost black, the bone-marrow is generally of a dark slaty colour. The small vessels are filled with endoglobular pigmented parasites, while numerous macrophages, containing pigment and red blood-corpuscles, may be found about the periphery of the lumina of the vessels. At times, between the corpuscles, Bignami (Atti d R.Acc.Med.di Roma, Anno xvi., v., 1890) found numerous ovoid bodies which, from their size and staining propensities, he believed to be free spores. Free pigment clumps are apparently yo be made out at times. Not only in the vessels, but also outside of these, the parasites are to be found in greater or less number. The macrophages are, however, especially numerous, even in the pulp.

There is little that can be considered as characteristic in other organs. The above description applies to the anatomical alterations observed in cases of acute malarial infections. We shall now consider chronic malarial cachexia - i.e., the changes following repeated or chronic onfections with the disease.

MALARIAL CACHEXIA.

The changes just described have to do with acutely fatal cases of malaria; and important pathological changes may occur in various organs and tissues, - e.g., the blood, spleen, liver, and bone-marrow, - as the result of long continued or frequently repeated attacks.

SPLEEN.

In malaria enlargement of the spleen is both constant and considerable. It may be of enormous size, reaching beyond the umbilicus and as low as the pubes. It is firm and hard, and its border is sharp. The capsule is usually much thickened, and white fibrous cartilaginoid plaques occur upon the surface. On section, the trabeculae are very prominent, and the organ has often a somewhat slaty colour. The acute splenic tumour is caused chiefly by the aggregation in the pulp of the spleen of an enormous number of red corpuscles, which have become either shrunken and brassy-coloured or decolourised, and are found included in the colourless elements of the spleen as brassy-coloured fragments or hyaline masses; by the continuous aggregation of colourless elements containing pigment, red corpuscles, or parasites, which collect from all parts of the body, and many of which are necrotic; and, thirdly, by great numbers of red corpuscles containing parasites, some of which apparently pass through the vessel walls by diapedesis, and seek the columns of the pulp, where they are for the most part enclosed by the epithelioid elements. While, as a result of this proceeding, a considerable number of the proper elements of the spleen become necrotic, others, as well as the pulp in the follicles, undergo karyokinetic division, while all this is followed by a marked hyperaemia and acute tumour of the splenic pulp. Thus the spleen is converted into a place for the deposit of débris, while processes of regeneration have begun to appear

at the same time during the same infection.The tissues in the neighbourhood of these collections of necrotic elements or those surrounding the necrotic areas of the splenic pulp,when the actual infection is at an end and the acute hyperaemia of the spleen has ceased,show certain changes which,on the one hand,tend to produce permanent alterations,and on the other to lead to a partial reparation of the part.In those parts where a considerable portion of the splenic tissue becomes necrotic,or disappears,being carried away by the lymphatics,the splenic vessels become considerably dilated,forming a netweork of venous lacunae which are separated by thin layers of pulp.This results in a tissue resembling that of an angioma.In those cases where a more marked destruction of the splenic tissue has occurred,and where every trace of the pulp is gone, parts become represented by extensive areas of tissue which consist of wide cavernous sinuses,the septa of which are composed of a very delicate connective tissue,rich in giant cells,similar to that of the bone-marrow.Some of the follicles become necrotic and fibrous.While this occurs a process of regeneration yet more extensive takes place,starting for the most part fromthe follicles,but also sometimes from the splenic pulp.The follicles become hyperplastic,reaching sometimes three or four times their normal size.This new form of lymphoid tissue,starting from the follicles, may be seen sometimes to surround necrotic areas of splenic tissue which become smaller and smaller and finally disappear.In the neighbourhood of these hyperplastic follicles occurs a hyperplasia of of the true elements of the pulp,while the reticulum becomes thickened so as to give rise,in preparations,to very beautiful and clear figures,such as are not to be seen in the normal spleen.The pigment,and probably the greater part of the necrotic elements,are carried on toward, and collected about,the periphery of the follicles,so that the diffuse melanosis of the pulp is followed by a perifollicular melanosis.The pigment then passes on into the lymphatic vessels of the sheaths of the arteries,and of the connective tissue of the septa.This results,on the one hand,in thickening of the vascular sheaths and of the septa,and,on the other hand,in the appearance - giving sometimes the picture of a lymphangioma and resulting in chronic lymphatic stasis - of single or multiple cysts.It is easy to understand the gradual development of the enormous splenic tumours - in which,sometimes,it is difficult to recognise the original structure of the organ,even under the microscope - when we consider that,after each new infection, fresh processes similar to these must occur.

LIVER.

In the same manner the anatomical alterations occurring in the liver in chronic malaria may be traced from those occurring in the acute infection.In the acute infection an enormous number of phagocytes,pigmentiferous or globuliferous,coming in great part from the spleen,invades the capillary network of the liver, while the parasites are generally scanty.The circulation is slowed,the capillary network becomes dilated,while

a certain amount of pigment is taken up by the endothelial cells of the vessels, and later by Kupffer's cells. The pigmented endothelium becomes swollen and in part necrotic. These vacular changes are followed by new areas of blood stasis. At the same time, as has been noted, many of the liver cells suffer alterations, either undergoing an acute atrophy from pressure, or a coagulative necrosis. These areas are sometimes quite extensive. In other instances many cells are found to be filled with blocks of yellowish iron-containing pigment, resulting from the early death of many red corpuscles. At the same time a certain number of hepatic cells, Kupffer's cells, and endothelial cells multiply by karyokinesis. Polycholia, an increase in functional activity, and acute hepatic tumour result from all this. But there is an escape of a small part of the great number of pigmented elements which enter the liver, passing through the branches of the suprahepatic veins. The greater part is taken up by endothelial and perivascular cells, so that the melanaemia is followed by a melanosis of the vessels. The pigment then passes forward out of the capillary network into the perivascular lymph channels, where it is collected in large blocks enclosed in white cells. These carry the pigment following the lymph channels to the periphery of the lobules, and perilobular melanosis follows thus the interlobular melanosis. Masses of the pigment are to be found, three or four months after the end of the infection, in large blocks, for the most part endocellular, in the perivascular lymphatic tissue of Glisson's capsule; and all this results from the extension of the process. There occur, on the one hand, permanent alterations, and, on the other hand regenerative processes while this migration of the pigment is going on. Where the dilatation of the lymph and blood-vessels and the degeneration and pigmentation of the vascular elements is most marked and extensive, no regeneration may follow the atrophy and necrosis of the endothelial and liver cells. The dilatation of the vessels increases, and becomes permanent. The greater part of the remaining liver elements disappears; only a few remain in an atrophic condition, the tissue showing an angioma-like appearance consisting of ectatic vascular network, about which may be recognised a stroma consisting of Kupffer's cells. Small lymphatic cysts may occur where the dilatation of the lymph vessels is most marked. An active regeneration of the tissue elements occurs about the atrophic or necrotic hepatic cells, in all parts of the liver, when the normal blood current has been restored after the disappearance of the pigment, and the necrotic masses in general, from the endothelial cells of the vessel walls. The young hepatic cells become arranged with great regularity in long rows on both sides of the old elements. Thus, when the stroma remains intact, an interlobular regeneration may occur. These regenerative processes are accompanied by the appearance of giant cells with budding nuclei, just such as are found in the embryonic liver. In parts of the liver that have not been freed from the collections of pigment and parasites, the regeneration never makes its appearance. A hyperplasia of the perilobular tissue follows the migration and collection of the pigment in this tissue, so that the surroundings of the lobules are more distinct. These degenerative and regenerative changes result, then, in a marked increase

in the size of some lobules and a diminution in size and atrophy of others.As this process accompanies each acute infection,one can naturally understand the chronic perilobular,monolobular hepatitis of malaria,which is characterised by the presence of zones of hyperplasia or of atrophy of the parenchyma,by chronic blood and lymph stasis,by the formation of areas of angiomatoid tissue,lymphectases,and lymphatic cysts.The large hepatic tumours,which are so well known,with smooth surfaces and lobules of irregular size originate in this manner.The changes in the liver may be described in four stages:(1)The organ appears congested,while the lobules are not sharply distinguishable and show in severe cases a decreased melanosis.The macroscopical characters are about the same as those of the liver in acute malarial infections.Microscopically,at this period,a little after the termination of the acute infection,it may be noted that the parasites have disappeared from the capillaries of the liver,the pigmented endovascular macrophages have in great part gone,and the pigment is entirely collected in the endothelium and in Kupffer's cells.These parts of the hepatic lobules in which necrosis or degeneration has occurred undergo a marked atrophy;the necrotic and degenerative elements are carried away in the phagocytes,while there occurs a dilatation of the network of blood-vessels.(2)On gross examination in a more advanced stage,the lobules are distinct.The melanosis continues to to diffuse throughout the lobule,but is more marked at the periphery.The organ is still congested.The particular features of this stage are that,on the one hand,the hepatic lobule frees itself from the accumulation of pigment and the necrotic remains,which become collected towards the periphery of the lobule,while, on the other hand,an active process begins by means of which a partial regeneneration of the parenchyma tends to take place.(3)The diffuse melanosis of the lobule, with the greater prevalence of pigment towards the periphery,is in this stage succeeded by an exclusively perilobular melanosis.The liver is enlarged,the consistency somewhat increased,and the surface smooth.On section,one may see that all the lobules are surrounded by a slate-coloured line,in the neighbourhood of which the colourisation of that part of the lobule is somewhat brown.In general,the slaty lines marking out each lobule form an exquisite network.The size of the individual lobules varies greatly;some are two or three times the normal size,others are markedly diminished.Microscopically,it may be observed that the degenerative alterations of some lobules have led to the formation of false angiomata,and of lacumae or cysts of lymphatic nature.Other lobules,by the process of regeneration already described,have increased notably in volume.The pigment has become extravascular;the white mononuclear and polymorphonuclear cells have effected its transportation through the capillaries and perilobular lymphatics.(4)The pigmentation is greatly diminished,and scarcely visible to the naked eye,in cases in which the acute infection has passed for three or more months. The liver is notably enlarged and congested.The surface is smooth.On section,one may see the lobules distinctly marked,surrounded by a most delicate reddish-brown

border;the consistency is somewhat increased.The melanosis will be seen to have become exclusively perivascular,if the microscope be employed.(5)One arrives, lastly,at the definite terminal form of the chronic malarial hepatic tumour.The macroscopical characters are the following:The liver is increased in size and in weight,sometimes enormously;the surface is smooth,the capsule a little thickened.On section,the appearance is finely granular,the lobules are distinct,a little prominent,and surrounded by a zone of slightly pinkish tissue.Microscopical examination shows the disappearance of all malarial pigment.The alterations of the parenchyma are similar to those described in the last two stages.The lobules of varying size are surrounded by a hyperplastic perilobular connective tissue.The connective tissue of the larger septa is,on the other hand,of about normal volume.A notable dilatation of the capillaries,with stasis of the colourless corpuscles, persists.The hepatic cells are altered in form in the zones where the dilatation is most marked.There is considerable difference in individual cases in the extent of these various lesions.There are cases,for example,in which,despite the enormous increase in the weight of the organ,there may be no very marked dilatation of the capillaries,nor are false angiomata or lymphatic cysts to be found,while,on the other hand,the hyperplasia of the perilobular connective tissue,and the increase in volume of many lobules,may be more marked; there may be an evident hyperplasia of the parenchyma - evidenced by hepatic cells with many nuclei and nuclei rich in chromatin substance.In other cases,on the other hand,one of the chief favtors in the enlargement of the liver may be the enormous development of the cysts and false angiomata.

BONE-MARROW.

The marrow of the long bones,- for example,of the femur in the upper and lower fourths,- is usually red, and of a consistency greater than is generally seen in acute infections,in the case of individuals who have had numerous relapses of malarial fever.The microscopical alterations are various;generally the signs of an active proliferation of the proper elements of the marrow are present.This leads to an increase in the haematopoietic activity.There are factors,however, such as the degenerative and destructive alterations which take place in the bone-marrow during acute infections,which injure,to a varying extent and through a varying length of time,the haematopoietic functions of the marrow.There may be cases in which the new formation of the haematoblastic marrow is wanting or entirely insufficient.The post-malarial anaemia is of necessaity progressive in these cases.Lastly,in other cases,very rare indeed,the bone-marrow presents the macroscopical and microscopical features which exist in acute pernicious anaemia,particularly the presence of a considerable number of megaloblasts.

BLOOD.

The changes in the blood in malarial fever are of great importance.They have been arranged in two categories - the first being due to to the direct action of acute malarial infection,and involving both

red and white corpuscles (pigmented globuliferous parasite-infected leucocytes), the other being secondary to the anaemic condition which is the result of the parasitic invasion. Among the first, the most important are the lesions of the red corpuscles caused by the action of the parasites, which develop within them and which are nourished at their expense. Some of these lesions differ according to the kind of malarial parasites, the gravest being found in the aestivo-autumnal fevers. But melanaemia is common to all forms of malaria and constant in that affection. In the tertian form especially, swelling of the red corpuscles is to be observed. The red cells are invaded by the parasites, and gradually increase in size until they are two, three, or even more times the usual size; at the same time they gradually lose their contour until they finally become pale, so much so that sometimes the corpuscles containing adult parasites, especially the forms known as gametes, are scarcely to be recognised by their outlines. They frequently are changed in shape, becoming more or less oval. Corpuscles which have lost their haemoglobin are seen, in fixed and stained preparations, to really contain the adult parasites which seem to be free in the plasma. The so-called brassy bodies described by Marchiafava and Celli (found in the aestivo-autumnal fevers, and only occasionally, as Bastianelli and Bignami have noted, in the ordinary tertian) best exemplify the shrinkage of the corpuscles with changes in the colour of the haemoglobin. The lesion may be designated as erythropycnosis, for the red corpuscle takes on the colour of old gold or of brass becomes smaller, and shrivels. Various conditions give the brassy bodies. They are especially to be met with in the apyrexia preceding a fresh febrile attack, when all, or nearly all, the aestivo-autumnal parasites in the circulating blood have become pigmented at the periphery, or have pigment in the centre, or a little excentrically. They may also be found after the administration of quinine, in which case many of the red corpuscles containing young, non-pigmented parasites are also brassy. In this latter event, we must believe that quinine in its final action determines a necrosis, not only of the parasite but of the red corpuscle containing it; and, in fact, after the lapse of time all these bodies disappear from the blood. Quinine does not, however, cause these changes in all parasite-infected corpuscles, for it not rarely happens that after its administration many free parasites are found in the blood, evidently having come out of the red blood-corpuscles. What becomes of the parasites contained in the brassy bodies - that is to say, previous to a febrile attack, independently of the action of quinine - is far more difficult to determine. It being known that all, or nearly all, the parasitic forms which reach the stage of multiplication are found stationary in the viscera, it is a reasonable certainty that the adult forms circulating within brassy bodies die with the corpuscle containing them: in other words, it seems probable that the necrosis of the corpuscle prevents the further development of the parasite. Followed, in all probability, by the death of the included parasite it is likely that the erythropycnosis represents a necrosis of the red blood-corpuscle; for we sometimes see parasites which have completed

fission within brassy bodies, though in such a case it is probable that the corpuscle has not long been brassy, but that the alterations in its condition occurred after the complete development of the parasite. In the aestival fevers, partial decolourisation of the red blood-corpuscles is not infrequently encountered. In some red globules containing bodies with blocks of pigment, we find the haemoglobin collected and, as it were, condensed around the parasite as though attracted to it, while the remainder of the corpuscle is seen to be more or less decolourised and usually shrivelled and wrinkled. In the crescent bodies, - which are surrounded by a thin layer of haemoglobin forming a sort of membrane around them, the rest of the corpuscle being recognisable only by its very faint outline, - this same condition of things is often to be found. The haemoglobin may be seen in some cases, - in which two bodies with central pigment masses are included within the same blood-corpuscle, - to form a certain kind of halo around each one, the globule being perceptible only by the delicate line at the periphery. This would lead us to believe that at the periphery of the corpuscle there is a stratum of tissue differentiated from, and more resistant than, the discoplasm, and forming a sort of membrane. In some cases, indeed, the parasite appears to be confined within a sort of bag, which is not well filled, and whose walls are withered and wrinkled. When an adult parasite comes out from a corpuscle, or a fission form is set free, and the spores disperse, this peripheral stratum appears to burst; at the same moment the haemoglobin is lost in the plasma. The fact that the pseudopodia, - even the large pigmented pseudopodia of the tertian parasite, - do not project beyond the surface of the red corpuscles may be due to the presence of this resistant peripheral layer. It is by no means infrequent to observe fragmentation of the parasite-infected corpuscles. Sometimes one sees a corpuscle containing, for instance, a pigmented aestival body, divide into two parts, forming two little corpuscles, in one of which the parasite - parasitiferous schistocytes - is contained. As explaining the stagnation of the corpuscles in certain vascular areas, great importance has been attributed to the changes in the physical properties of the parasite-infected corpuscles. A tendency to agglutination on the part of the red corpuscles which were not infected with the parasites was observed by Bignami in only two cases of haemoglobinuria. This author, when studying the distribution of the parasites in the vessels of the various viscera in pernicious fevers, noticed that the parasite-infected red corpuscles, in the veins of certain calibre, showed a tendency to place themselves against the walls of the vessels, and that sometimes they would gather in one vein, being grouped together as if agglutinated. This circumstance he endeavoured to explain by assuming a diminished elasticity in the discoplasm, and a qualitative alteration in the surface which had apparently become viscous. Red corpuscles containing aestivo-autumnal parasites, especially when these are adult bodies, are less adapted than normal ones to the circulation on account of this fact. This has been proved by actual research. If an ordinary fresh preparation of aestivo-autumnal blood, in which are numerous corpuscles containing bodies with blocks of pigment, we cause a current by pressure, we shall see that the corpuscles containing

the above-mentioned bodies scarcely move,and appear almost to cling to the glass.Less elasticity and a greater viscidity than normal may therefore be presumed for many of the corpuscles,even those which present no alterations recognisable under the microscope.In malarial cases,by far the most characteristic alteration in the blood is melanaemia;which same,at least so far as we are aware,occurs only in this disease and is pathognomonic of it.It consists in the presence in the blood of a pigment,- the determination of which is easy if a thin layer of blood be subjected to microscopical examination,- of a brownish or black,or brownish-yellow or reddish-brown colour,which occurs in the form of granules,rods,needles,or blocks,the joining together of which gives conglomerations of greater or less size. In rare cases they are free;but,as a rule,they are included within the body of the malarial parasite or in the leucocyte.In former times it was thought that this pigment was derived from the colouring matter of the red blood-corpuscles;and many were the opinions held thereon.As earlu as the century before last,some physicians observed that various organs were of a black or dark appearance in grave malarial fevers.Particles of black pigment were first observed in the blood by Meckel,who said that they came from the spleen.The term"black spleen" was invented by Tigri to describe the melanosis in connection therewith.The hypothesis that the pigment originated in the spleen was advanced by Virchow,who noticed numerous pigmented cells in the blood of a man who had died with dropsy after many attacks of intermittent fever.To him and Frerichs we owe the theory that melanaemia represents a dyscrasia due to the alteration of some organ.To the latter observer we owe an accurate description of melanaemia,and of its effect upon the organism.He observed in the blood free black granules and molecules,and pigmented cells resembling leucocytes,now fusiform and now cylindrical in shape;accumulations of black granules,held together by a pale substance,or having an involucrum of a hyaline substance which was sometimes thick and sometimes thin,were also described by him.Frerichs believed that the pigment was formed in the spleen,because,first, pigment is found in the normal spleen;second,in melanaemia there is always more pigment in the spleen than in the general circulation;and,third,in the general circulation we find pigmented splenic cells.He held, moreover,that sometimes even the liver might participate in the formation of pigment.He agrees with Virchow that in intermittent fevers the pigment enters the circulation after its formation in the spleen.As to the method of its formation,Frerichs thought that in malarial hyperaemia of the spleen the blood was poured in large amount into the lacunae of this organ,stagnated there,and was there destroyed,whence the formation of masses of pigment from the haemoglobin of the red corpuscles.That this formation of pigment does not occur in hyperaemia of the spleen from other causes is because chemical changes of the splenic juice are produced in malaria which menace the existence of the red blood-corpuscles.Meigs lays stress upon the intimate connection existing between the formation of black

pigment and intermittent and remittent fevers, stating that he has looked in vain for the same conditions in other diseases. He notes the marked diminution in the number of the red corpuscles during acute infections, and accurately describes the condition of the viscera in the cadaver, dwelling upon the characteristic aspect of the various nervous centres in which, as a rule, the pigment is found in minute granules within the capillaries, sometimes in such abundance as to modify the colour of the nervous tissue. He affirms that the pigment granules are found within cells not to be distinguished from leucocytes or splenic cells; but sometimes the pigmented cells have an oblong or spindle-shaped outline. In the splenic pulp he claims to have found red corpuscles in various stages, not only of disintegration, but of metamorphosis into true pigment; so that he holds with Frerichs that it is from the haemoglobin that the black pigment originates. The latter is most abundant in spleen and the portal vein, but in grave cases it is found in the whole organism. On the other hand, however, Colin insists that the formation of the pigment occurs not only in the vessels of the spleen, but also in those of other organs; but he also asserts, without giving sufficient reasons for this belief, that this formation of pigment has nothing specific in its nature, because it occurs in other diseases as well, for instance, in the mesenteric glands in typhoid fever and dysentery. On account of the more rapid and more marked destruction of red corpuscles, he holds that in malarial infection, however, the condition is more conspicuous than in other diseases. The theory of the primary formation of the pigment in the spleen, advanced by Virchow and Frerichs, is supported by Mosler, who holds that the special structure of the spleen lends itself to the formation of the pigment - that is to say, that the blood flowing from the capillaries into the intermediate blood-vessels not rarely stagnates there, so that conglomerations of red corpuscles occur which gradually become converted into pigment. In the enlarged spleen of malaria he believes, with Frerichs, in the occurrence of a chemical change in the quality of the splenic juice. In this particular, Arnstein's researches are important. He maintains that the pigment is formed in the circulating blood during the febrile attack, and is deposited by it in the spleen, liver, and bone-marrow. He observes that the pigment is found in the blood free or included in white corpuscles, - which is the usual occurrence, - during the fever or shortly after. On examination of such organs as are most melanotic, - the spleen, bone-marrow, and liver, - he finds that they contain pigment not only in the blood-vessels, but also around them, and only in cases of recent infection does he find it in other organs, such as the brain and the kidneys. He holds that the theory of Virchow and Frerichs is not tenable, but believes that the melanaemia - the presence of black pigment in the circulating blood - is the primary occurrence, and the melanosis of the spleen and liver secondary: indeed, melanaemia may be found only for a short time after the febrile paroxysm, which would not be comprehensible of the melanosis of the spleen were primary; furthermore, the deposition of the pigment

in the circulating blood correspknds perfectly with what occurs when one introduced within the circulation such a colouring matter as cinnabar.Therefore,during the febrile attack the rec corpuscles,according to him,are destroyed,and the pigment which is formed is rapidly taken in by the leucocytes which stagnate in the veins and capillaries of those organs in which the circulation is slowest,- that is to say,the spleen,the liver,and the bone-marrow,- whence the pigment is deposited in the tissue of these organs.As to the mode of formation of the pigment,he admits that he has no knowledge,not having been able to follow the process of disintegration of the red blood-corpuscles through all its stages.He holds it to be probable that the pigment is formed in the blood serum from haemoglobin which has come out of the red blood-cells.He does not believe that the pigment is formed within the leucocytes,as Langhaus observed in haemorrhages,because we find free pigment in the blood and no globuliferous cells.These are few in comparison to the enormous amount of pigment present in the circulating blood,and are,however,found in the spleen and in the bone-marrow.These opinions have been upset by more recent investigations.Kelsch, speaking of the melanaemia,desfribes in the blood of malarial patients,especially those suffering from pernicious fevers,the presence of free pigment,or pigment included in hyaline masses,or more often still in white corpuscles.He notes that there are melaniferous elements which contain pigment granules arranged in wreath form; he describes others which give a brownish reflection in the marginal zone,and contain fine black granules; and in the blood of the splenic and portal veins he found melaniferous cells which were most varied in form and size,being spherical,polyhedral,ovoid,elongated, biscuit-shaped,etc.As to the distribution of the pigment,from a study of the various organs in patients who had died of pernicious fever,Kelsch comes to the conclusion that it behaves exactly in the same way as granular colouring matter injected into the circulation. In opposition to the theory of Virchow and Frerichs,he believes that it is formed in the circulating blood:in fact,in a case of fulminating pernicious fever he found little pigment in the spleen,while the blood was filled with it.As to the mode of formation,he cannot admit that any of the elements represent the stroma of decolourised red cells with pigment granules formed at the expense of the haemoglobin,because he did not succeed in finding the intermediate stage of this retrogressive metamorphosis;nor does he admit Langhaus's theory of the intra-cellular formation of pigment,because the pigment is also found free in the blood.He takes refuge in the hypothesis - which applies also to what occurs in the blood on the injection of cinnabar - that the melanotic material proceeding from the destruction of the red blood-corpuscles exist in the serum in a state of solution,and when the blood becomes saturated is precipitated in the form of granules which are speedily taken in by the leucocytes.As early as 1879,Marchiafava suspected that the pigment was formed within the red blood-cells,and subsequent researches have confirmed his conclusion anent it.From his study of the splenic

pulp,and of the bone-marrow in melanaemic children,he came to the conclusion that the red blood-corpuscles do not give rise to the formation of pigment after their disintegration;but that,on the contrary,the conversion of haemoglobin into melanin occurs by degrees within the corpuscle itself.Afanassiew,having doubts as to the origin of the pigment from the red corpuscles, suspected the parasitic nature of the pigment granules, and held them to be analogous to the Micrococcus chromatogenus of Cohn.The theory of melanaemia was definitely established,however,by Laveran,Richard,and Marchiafava and Celli.The first-mentioned observer's researches,while they led him to assert the parasitic nature of the pigmented bodies Nos.1,2,and 3,did not lead him to an exact recognition of the genesis of melanaemia. In fact,not having observed progressive endoglobular development of his pigmented bodies,he was inclined to believe,at the beginning of his researches,that the pigment was an integral part of the parasitic body:so much so,indeed,that in the waters of malarial regions he sought a pigmented parasite,but not finding it,he advanced the theory that a destruction of red blood-corpuscles might give rise to the pigment.It is probable that,in spite of all contradictory evidence,these long series of researches have proved(especially the observations of Arnstein and of Kelsch) that the black pigment is formed in the circulating blood,and that, consequently,the melanosis of such viscera as the liver and spleen is secondary to the melanaemia;but that the genesis of the pigment is still uncertain.It is obvious that,except by a methodical study of the alteration of the red cells preceding the formation of the black pigment,no convincing solution of the question as to whether the pigment was formed in the serum from colouring matter which had escaped from the red corpuscles,-as Arnstein believed,or whether the melanotic substance did exist in the plasma in a state of solution and become precipitated when the plasma was saturated;and also if it was a part of the body of the parasites,or was its formation from the red blood-corpuscles determined by the action of the parasites.This subject was thoroughly investigated,in 1883,by Marchiafava and Celli,who came to the conclusion,reached by Marchiafava a few years previously,that it is within the red cells themselves by degrees that the conversion of haemoglobin into melanin occurs,and that the red corpuscles do not give rise to the formation of pigment after their disintegration.The appearance within the cells of spherical or ring-shaped bodies,easily stained by some of the analine dyes,-e.g.,methylene blue,-was seen by these authors to usher in the changes started by the red corpuscles and leading to maelanaemia. In these little bodies,which,as the substance stainable by methylene blue increases,increase both in size and number,small granules of pigment begin to appear sunsequent to this alteration.From all this,these authors were able to assert that the formation of pigment occurs within the red cells which have already undergone characteristic alterations,and this even before they had recognised the parasitic nature of the little bodies which could be stained by methylene blue;so that all previous theories became untanable.The theory of

melanaemia became cleared up on the establishment of the parasitic nature of the spherical and annular bodies.It is intimately connected with the life cycle of the parasite:so much so,indeed,that a description of the genesis of the melanin cannot be separated from that of the malarial germ itself.In the various vascular areas during an acute infection,the distribution of the grains and blocks of melanin corresponds in the same manner finally to the distribution of the parasites. This explains the fact that the distribution does not altogether correspond to that of inert powders injected into the blood,as Kelsch maintained,although,as a rule, it resembles it greatly.For instance,the melanosis of the brain in comatose pernicious fevers,and the sometimes enormous accumulation of pigmented parasites in the intestinal capillaries in choleraic pernicious fevers,are facts which it would be impossible to understand unless we bear in mind that we have to do,not with free circulating pigment granules,but with pigmented parasites.Therefore,the morbid anatomy of pernicious fevers furnishes the law of distribution of the black pigment.Regarding the successive changes which occur in the formation,by parasitic action within the red cells,of melanin from haemoglobin during an acute infection, we have seen that when fission of mature parasites is fairly accomplished,a residuum of segmentation of left,formed chiefly of a lump of melanin or an accumulation of black granules.When disaggregation of the spores has occurred,the pigment becomes free in the plasma,and thence is quickly taken up by the leucocytes and in part by the endothelium,especially in certain organs.The latter process is well seen in the brain and in the liver.This process occurs with every species of malarial parasite.But it is not only from the multiplying bodies that the pigment found within the leucocytes and the endothelium is derived.In part it comes from the parasite-infected red corpuscles which die before the development of the parasite is complete, in part also from the pigmented parasites that may escape from the red corpuscles and so become free in the plasma.The first occurs chiefly in aestivo-autumnal fevers,in which,as we have seen,many corpuscles (red) become brassy;both brassy corpuscle and included pigmented parasite may be taken up by a leucocyte.The second is somewhat frequently noticed in the tertian,in which we may find free pigmented hyaline spherical bodies in the plasma,which are parasites,or fragments of parasites,that have come out of the red blood-corpuscles.Finally,all the pigmented bodies which in man are sterile,- forms of the anophelic cycle,- end by becoming included when they cannot continue their regular development outside the human body.The free or included pigment then accumulates in certain viscera, spleen,liver,and bone-marrow,just as do inert powders injected into the circulation.But it is to be remembered that in these organs a large amount of pigment is formed in situ,or within their vascular areas,especially in aestivo-autumnal infections,because of the fact - already emphasised - that it is precisely within the vessels of the spleen,etc.,that the adult forms of the parasite accumulate and complete their development,

during which process they form a notable amount of pigment.Little by little,the black pigment is seen,in these same viscera in which it has accumulated,to become transformed and destroyed;so that the melanosis entirely disappears in a short time after the cessation of the infection.The exclusive derivation or otherwise from the melanin elaborated by the parasite of the black pigment,- which accumulates in the viscera,sometimes to an enormous extent,in persons who have had several attacks of fever,- is a question which has been the subject of considerable discussion.It is now belived that the melanosis of the viscera is chiefly the result of the melanaemia,that is to say,it is the result of the black pigment formed,during acute infection,in the circulating blood.In part it has a local origin,that is to say,it is derived from the slow transformation of the lumps of yellow pigment which are deposited or formed in the spleen and other organs from altered red corpuscles,which in grave infection die before the direct action of the parasite has transformed their haemoglobin into melanin.Schmidt,so we are informed by Neumann, was able to demonstrate by actual experiment that this transformation of haemosiderin into a black pigment is one that does not give the microchemical reactions of iron.The chemical composition of melanin is but little understood,although its origin is known.Marchiafava and Celli noted the fact that even the finest of the black granules formed within the red corpuscles,and indicating the earliest stage of the transformation of the haemoglobin,do not give a microchemical reaction of iron;and upon this point all authorities agree,Carbone,as a result of the chemical analysis of the pigment of a melanotic spleen,came to the conclusion that malarial melanin is for the greater part idenitcal with haematin.This does not absolutely exclude the possibility of there being other pigments included with the haematin,although he maintains that this is not very probable.Such a chemical composition of melanin would be quite in harmony with what is known in regard to its origin.We know, in fact,that haematin is a product of the digestion, both gastric and pancreatic,of haemoglobin;and it is therefore natural enough that the malarial parasite, when absorbing the haemoglobin of the red corpuscles, should also give out haematin as a product of intracellular digestion.In other words,we may suppose that the parasite is nourished by the abstraction of the albuminoid constituents from the complex molecule of haemoglobin,leaving the pigmented portion,that is to say,the haematin,unused.According to these researches, then,melanin is a transformation product of haemoglobin, containing iron,but not in one of those combinations in which it is demonstrable by means of microchemical reaction.It is generally believed that the melanin is found only in malarial infections.Dealing with the question as to whether there is a malarial infection without melanaemia,Marchiafava and Celli affirm,as a result of their researches,that they are inclined to the belief that this is the case,having seen cases in which the parasite accomplished all its life cycle,up to fission,without being pigmented.Many other writers, taking these observations as their basis,speak of a

variety of malarial infection,caused by a parasite of the red corpuscles,which did not produce pigment.Still later,others began to doubt the exisfence of a form of malaria without melanaemia,having observed that,even in cases in which an examination of the peripheral blood showed only non-pigmented parasites and in the brain non-pigmented fission forms,in the spleen there were both pigmented parasites and pigment included in leucocytes.An endoglobular parasite,which completes its whole cycle of existence without the production of pigment,has been described by Dionisi.The existence of an infection produced by parasites of the red corpuscles which complete their life cycle without producing pigment is a well-established fact,indeed,in the case of certain animals,the important instance of this being that of the so-called Texas fever of cattle.In the case of the human being,however,it is certain that of late years,in spite of the great abundance of material,no one has ever seen a case of malaria without melanaemia. We find in the viscera of malarial patients,in addition to the black pigment,another pigment in the form of yellow or dark yellow granules or lumps:this is the ochraceous pigment,the distribution of which has been reported upon by Kelsch and Kiener,Guarnieri,Bignami, and others,who affirm that it may be found in large amount in the liver and the spleen,in less amount in the bone-marrow,and scantily in the kidneys.In contradistinction to melanin,this pigment gives the iron reaction with microchemical reagents,and is identical with the haemosiderin of Neumann.It may be found in the liver included within the endothelium of the blood-vessels;but the larger part of it is in Kupffer's cells and the hepatic cells,differing in this from melanin which is never found in the epithelium of the liver. Frequently the pigmentation is the mst intense around the central vein,and shades off towards the periphery of the hepatic lobule.In some pernicious fevers this haemosiderin is so intense and so diffuse that it is more marked than the black pigmentation of melanin. The formation of bile pigment evidently uses up all this haemosiderin in the liver.The yellow pigment is found in the spleen within the globuliferous cells or free in the splenic pulp;in chronic tumours ir is also seen,sometimes in large amount,within the vessels and splenic septa,being evidently deposited along the lymphatic tract.In the case of the kidneys,in rare instances only,we see granules of haemosiderin within the epithelium of the tubules,especially in that of the convoluted ones.The indication for the presence of this yellow pigment,in the viscera of persons who have died of pernicious infection,clearly is that not all the haemoglobin of the destroyed red corpuscles is transformed into melanin by the action of the parasites,but that the acute infection determines the disintegration of a variable number of corpuscles by means of some other mechanism.Mention has already been made of the brassy bodies,which are the product of early necrosis of the red blood-corpuscles,occurring while the parasites are still in process of development.In this alteration of the red corpuscles we see one source of the haemosiderin deposited in the cells of the viscera;and perhaps it is the chief source during the acute infection.But we are unable to affirm that all the iron-containing pigment,which is sometimes so abundantly present

in the viscera of patients with chronic malaria and cachectics, has the same origin. Above all, in grave post-malarial anaemic conditions we mat find an abundant ochraceous pigmentation of the liver as in some cases of pernicious anaemia. Now, as we know that this anaemia may sometimes continue, and even progress autonomously without relapses of fever or fresh parasitic invasions, we are forced to the conclusion that the pigment of haematic origin is in this case formed by the action of some haemolytic substance as yet unknown.

Now regarding the changes in the leucocytes in malarial fever, we may note that the attention of investigators from the earliest days of research has been attracted to the presence of leucocytes containing granules or blocks of pigment. We have already seen that the discovery of the malarial parasite was preceded by a series of researches, one result of which was to distinguish the pigmented leucocytes from other pigmented bodies differing from them, namely, the large pigmented bodies. With this increase in knowledge of the biology of the parasite came a corresponding increase in the comprehension of the phagocytic processes which occur in malarial blood. The black pigment was held by Laveran to be taken up by the leucocytes after the disintegration of the parasites. Later, Marchiafava and Celli established the fact that the white cells cab take in not only pigment, but whole parasites and parasite-infected red corpuscles, and observed that the whole phenomenon of phagocytosis may also occur, in vitro, in ordinary preparations of blood, so that we may witness the struggle even under the microscope. They noted, moreover, that the vascular endothelium also plays an important part in phagocytosis in malaria. The importance of the part taken by macrophagi in the liver and spleen was later pointed out by Metchnikoff. In the case of tertiam and quartan fevers phagocytosis was studied by Golgi, who discovered that the pigmented leucocytes are to be found in the blood in the early hours of every febrile attack, and concluded that phagocytosis occurred regularly in correspondence with determined phases in the life of the parasites. He attributed great importance to the phagocytic action of the leucocytes, holding that to it is due the spontaneous cure of malaria, as others believed; and he even went so far as to assert the probability that the fact of not all the malarial parasites becoming pernicious is due to this process. Guarnieri investigated the question of phagocytosis in the liver; and Bignami extended his researches to the various viscera in pernicious fevers; and both describe the occurrence of phagocytosis leading to the degenerative changes which occur in the leucocytes and in the endothelium. Regarding the elements which play the part of phagocytes, these are (a) some, but not all, of all the varieties of leucocytes which are in the circulating blood; (b) the endothelial cells and the cells of Kupffer in the liver; (c) the cells of the splenic pulp; and (d) the large uninuclear leucocytes, without granulations, in the bone-marrow. (a) The chief rôle in the phagocytosis during the febrile attack belong to the leucocytes in the circulating blood; but not every kind of leucocyte has a phagocytic function. Although the observance

of small pigmented leucocytes, in rare cases, has been claimed by Vincent, Guarnieri and others have noted that the lymphocytes never contain black pigment. The large uninuclear leucocytes without granulations, and the so-called transitional forms are generally believed to be the most important agents in this process. Next in order come the ordinary leucocytes with polymorphous nuclei, and neutrophile granulations - multinuclear leucocytes; the fact that the greater part of the phagocytes found in malarial blood belong to the group of macrophagi of Metchnikoff follows from the fact that neither the lymphocytes not the eosinophile white corpuscles perform phagocytic functions, and because it is altogether exceptional to find a pigmented eosinophile leucocyte. In ordinary malarial infections the total number of leucocytes diminishes to below normal, while in pernicious fevers it is increased. But the fact is also worthy of note that the numerical proportion between the various kinds of leucocytes is more or less markedly modified; that is to say, there is an increase in the large uninuclear leucocytes and the transitional forms, and a diminution in the number of of the polymorphous leucocytes, while the number of lymphocytes remains at about normal. This modification in the numerical relation between the large uninuclear leucocytes and those with polymorphous nuclei is found in the ordinary infections -tertian, quartan, aestival, as well as in the pernicious forms: in the last-mentioned, however, the increase of the large uninuclear cells chiefly attracts attention, while in the first attacks of a primary infection it is the least marked. The large number of macrophagi found in some cases is a matter of astonishment to all who have examined the blood in pernicious fever; and, indeed, the increase in the number of the large uninuclear leucocytes is much more noticeable in grave malarial infections than in those conditions, such as grave anaemia and hyponutrition of the organism, in which, as Ehrlich has shown, the same thing occurs. In malarial blood there is an increase of precisely those elements which play the chief part in phagocytosis, namely, the large uninuclear cells. These bodies enter into the circulation in a larger number than normal, evidently by a process of chemotaxis; or, in other words, for the same reason that in other morbid conditions multinuclear leucocytes are poured into the blood. The chemotaxis is specific, and is exercised nu determined substances upon a particular species of leucocyte: in fact, if an individual in whom malaria alone has determined a percentage increase in the large uninuclear cells, there occurs some inflammatory process, such as pneumonia or erysipelas, the multinuclear cells in their turn increase in the blood - inflammatory leucocytosis - under the influence of the specific action of Fraenkel's diplococcus or of the streptococcus. (b) It is only during the course of the gravest infections that the pigmented endothelial cells are found circulating in the blood; they evidently become detached from the vascular walls, as a result of the alterations which they undergo after the inclusion of the foreign bodies which they take up. A minute investigation of the viscera can alone give us an exact idea of the extent to which this fumction of

the endothelium is exercised.In some cases the number of pigmented endothelial cells in the brain is remarkable.It is eveident that the accumulation of adult parasites in the cerebral vessels,and the resulting relative slowness of the circulation,favour the development of this function.But while this function of the endothelium helps to free the blood-vessels from injurious matters; on the other hand,lesions of the vascular walls,which increase the difficulty of the capillary circulation and contribute still further to its retardation,are produced by the degenerative changes which follow phagocytosis.A phagocytic action of the endothelial cells is observed even in the liver;indeed,the pigmentation of the endothelium persists longer than does the presence of melaniferous leucocytes within the capillaries after the active infection has ceased.To this Bignami testifies;and the same thing has been noticed in the case of Kupffer's cells by Guarnieri,who says that he found in them not only the black pigment,but grains and clumps of haemosiderin or yellow pigment in variable amount,but in pernicious fever in considerable quantity. (c)In all acute malarial infections the cells of the splenic pulp take an active part in phagocytosis.This is demonstrated not only by pathological studies in pernicious fevers,but also by the examination of the splenic contents extracted by puncture in cases of ordinary fever.The number of pigmented globuliferous and parasite-containing macrophages is truly enormous in grave infections;but no included bodies are ever found in the lymphocytes of the Malpighian follicles. The blood of the splenic vein is rich in pigmented macrophagi or the débris of red blood-corpuscles,for which reason it is believed that it is from the splenic pulp that a large number of similar elements which accumulate in the capillary network of the liver are derived.(d)Not only within,but also outside of the blood-vessles of the bone-marrow,- especially of the spongy bones,- phagocytes of similar histological character are also found in the majority of pernicious fevers.It is certain that some of these elements are derived from the blood which deposits them in the large medullary veins;but everything points to the belief that in large part they are medullary cells which have exercised a phagocytic function in situ.That in the spleen and in the bone-marrow - and,according to Ehrlich and Lazarus,chilefly in the latter tissue - there originates in this way the large uninuclear cells without granulation,- the chief elements in malarial phagocytosis,- is a fact that is now beyond dispute. It follows from all this that phagocytosis occurs in the whole vascular system during acute malarial infections, but chiefly in certain viscera,and precisely in those whivh,as experimental pathology teaches us,are deposited the corpuscular extraneous substances injected into the circulation,namely,the spleen,liver,and the bone-marrow. After cessation of theacute infection the phagocytes which have gathered up pigment or parasites elsewhere are also deposited in the organs,which participate actively in the process by means of their own cells - large uninuclear cells without granulations of the bone-marrow,and cells of the substance of the spleen.

There are various kinds of substances which may become included in the cells.The clumps of pigment and the residua of degmentation,which remain free after the multiplication of the parasites come first in the order of frequency;less often we find complete fission forms, either free or iwthin erythrocytes,or isolated spores. This occurs in tertian and quartan,as wel as in estival fevers.Even in aestival fevers,the parasites bring about certain changes in the physical properties of the red corpuscles,which in all probability favour the appearance of the function of phagocytosis - e.g.,as a certain viscidity of their surface.As to the young forms and those in process of development,it is to be noted that this only in the aestivo-autumnal fevers do they become included in phagocytes to any marked extent; the reason for this is found in the early alterations undergone by the parasite-infected red blood-corpuscles in this group of fevers:In fact,we find included, in the order of frequency,parasites with central pigment or peripheral granules of pigment,or even non-pigmented young forms contained in brassy or pale corpuscles;very rarely,parasites in various stages of development,contained in corpuscles in which the methods of examination at our disposal do not permit with any certainty of the recognition of any alteration.It is rare to find,however,any young parasites within the leucocytes in the case of tertian fever.The pigmented hyaline spherical bodies,which originate from parasites that have come out of red blood-corpuscles and have in the plasma become disintegrated, have been seen by Bastianelli and Bignami included in the leucocytes in the spleen of tertian-fever patients.From this it is evident that phagocytes may take in not only the adult and actively multiplying bodies,which in the process of multiplication leave the red corpuscle and become free in the plasma,but also forms in process of development and young bodies,whenever the red corpuscles which contain them undergo some early and profound change which causes them to behave towards the phagocytes like foreign bodies in the blood-current.The reason why the phagocytosis of the parasite-infected red corpuscles is of great importance only in the group of aestival fevers is obvious from this early necrosis of the red corpuscles occurring with regularity in aestival fevers and only exceptionally in the others.The phagocytes,in addition to these bodies,may take up the adult forms incapable of multiplying in the human organism,that is, the gametes.When the latter remain in the host,they go on to those degenerations which were recognised before their subsequent development in the intestine of the mosquito was understood.We find a variable number of fragments of red corpuscles,which by further transformation of the haemoglobin give rise to grains or clumps of haemosiderin,in the phagocytes,especially such as are situated in the viscera.In the spleen and liver,especially in the endothelium and in Kupffer's cells,this occurs extensively in the case of certain pernicious fevers.In short,phagocytosis acts,first on substances which originate from the parasites,that is to say,the black pigment and the residua of segmentation;second, on the parasites themselves when they become free in the plasma,or when they are contained within much altered,red blood-corpuscles;and,third,débris of red corpuscles and entire dead cells.Phagocytosis is

escaped by the parasite-infected red corpuscles which have not been specially changed. Evidently a chemotactic action between the phagocytes and the substances which they take up - an action which is developed only under the conditions mentioned - gives rise to the phenomenon. There are various modifications which the included substances undergo. The haemoglobin of the amoebiferous red corpuscles goes through the changes which have been described until the latter are mere shapeless rusty masses. The melanin, which in the leucocytes of the peripheral blood is found in grains or needles or distinct blocks, becomes gathered into large formless masses. These are usually found in the phagocytes of the spleen and liver, while in the circulating blood they are seen only in grave infections, chiefly in pernicious fevers. As to the included parasites, they remain clearly recognisable, and capable of staining, so long as the red blood-corpuscles, with which they have been absorbed, persist. The free bodies apparently change and disintegrate very rapidly after their inclusion, so that it is difficult to recognise them; only the fission forms, the bodies with blocks of central pigment, and also the free spores, maintain for a length of time, as yet undetermined, their normal capacity for staining. It will not be possible to recognise parasitic bodies within the leucocytes, however, if a spleen be examined, with even the best colouring matters, not so very long after the cessation of an acute infection. It is probable, then, that all the parasites included in white corpuscles are destroyed with more or less rapidity, and become incapable of further development. Only as to the spores, which remain recognisable longer then do the other parasitic bodies, Bignami advances the theory that they may persist alive and take on a new development after necrosis of the white cells which contain them. He also further supposes that the said spores, which are naked in the beginning, may later become surrounded by a membrane, and thus, when still within the leucocyte, escape our methods of staining and demonstration. It is impossible at the present time to refute these hypotheses advanced for the explanation of the period of latency, although they have recived no confirmation from the researches of others. The theory of Golgi and Monti, that the aestivo-autumnal parasites are capable of continuing their development within the leucocytes or the tissue cells, may, however, be positively excluded; and opposed to it are all the arguments derived from probability and analogy. The chief argument in support of this theory is the fact that within the phagocytes may be found every phase of the parasite from the youngest to that of sporulation; yet, as has been already mentioned, the number of young parasites included is small in comparison with the number of bodies with central pigment or in fission; so that it is erroneous to assume that the adult bodies come from the parasites which have been included in the leucocytes from the earliest stage of their existence. On the other hand, direct observation shows that most of the parasites become included only in the later stages of their life cycle which had developed normally within the red blood-corpuscles. Degenerative changes, which may go on to necrosis, frequently occur in the leucocytes as well as in the other cells that have acted as phagocytes. These

alterations may be seen in the leucocytes which are found in the peripheral blood only in grave infections and in pernicious fevers;as a rule,however,they are seen also in the spleen,liver,and bone-marrow,where, indeed,there is an abundant presence often of the degenerating and necrotic elements.Fatty degeneration and nuclear changes are the principal alterations to be observed.The former attacks chiefly the large uninuclear leucocytes,and usually after they have taken in a large number of foreign bodies;they then appear as large cells,even two,three,or more times the normal size of an ordinary leucocyte,which contain in their protoplasm a large number of spherical shining bodies of various sizes,which in fresh preparations are sometimes oscillating,which disappear in dried preparations, are not stained by aniline colours,and are not visible in sections fixed in alcohol.A similar degeneration may be be seen,although rarely,in leucocytes which do not contain other bodies.Bignami found the same change, in some cases of acute malarial infection,in the endothelial cells of the spleen and liver,and in Kupffer's cells.For the most part these little spherical droplets are of a yellowish colour;sometimes the yellowish colouration is seen throughout the whole cell,suggesting a slight imbibition of haemoglobin,such as has been noted to a greater or less extent in the leucocytes in certain cases of intoxication by haemolytic poisons such as pyrodin.This special form of alteration may be studied in preparations fixed in osmic acid;in them we note that the granules or droplets scattered scattered in the protoplasm have generally only their outlines darkened.Although they would appear to be fat droplets,- from their other properties such as solubility in alcohol and ether,- this fact makes it difficult to determine their exact nature.It is the macrophagi that, as in the case of fatty degeneration,are chiefly attacked by vacuolisation:in this case also,the cell is swollen,and the protoplasm appears to be rarefied by the presence of numerous vacuoles,in some of which we may seeincluded bodies.This alterations may also be seen in circulating blood,especially in grave cases of aestival fever.The nucleus may sometimes show retrogressive changes;in other cases in the leucocytes with vacuoles,as in those with fatty degeneration,the nucleus often remains of normal appearance in stained preparations.We often do not see it present at all, however,in fresh preparations;and we are surprised to see these protoplasmic masses of occasionally enormous size,filled with vacuoles,without perceptible nuclei, and sometimes presenting active amoeboid movements,when examining a fresh specimen at a temperature above 85° F. Preparations fixed in absolute alcohol and ether,and stained with haematoxylin and eosin,show well the nuclear changes.Sometimes the nucleus is fragmented in irregular masses,which become intensely stained in a somewhat uniform manner - nuclear fragmantation and chromatolysis.At other times only the membrane of the nucleus is recognisable,the nuclear chromatin having disappeared,and the whole nucleus is but faintly stained.From this change,a series of transitional stages lead up to the phagocytes which present all the signs

of necrosed elements, that is, coagulation necrosis; they are formless masses of protoplasm, with irregular outlines, without trace of nucleus, staining faintly, and sometimes dotted with irregular small bodies that are stained with haematoxylin, and represent residua of the nuclear chromatin. In preparations from the spleen, we see also protoplasmic masses of varying size, without recognisable cellular structure, formed, it is believed, by the necrotic phagocytes undergoing fragmentation. The endothelial cells present similar alterations. While many phagocytes undergo these retrogressive changes, which partly account for the leucopania observed during the febrile attack of malaria, other cells multiply actively in the haemopoietic organs. Multiplication by karyokinesis of the endothelia and Kupffer's cells has been observed by Guarnieri and Bignami in the liver: the latter further described the multiplication by karyokinesis of the cells of the splenic pulp, and of the large uninuclear leucocytes of the bone-marrow. The new elements replace those which have become necrosed from the exercise of their phagocytic function. It is to be noted that the cells in karyokinesis are, as a rule, non-pigmented. In pernicious infections, karyokinesis of leucocytes may occur even in the circulating blood, as has been observed by Bastianelli and others. The process is exactly similar to that seen in the splenic pulp and in the bone-marrow. In some pernicious fevers these forms are somewhat numerous, two or three being found in one preparation; but they are always less in number than in preparations from the splenic pulp. By this active proliferation the haematopoietic organs provide an abundant supply of new large uninuclear leucocytes, of those elements which are of chief importance in malarial phagocytosis. As in grave anaemic conditions erythroblasts in mitosis may issue from the haematopoietic organs, a similar thing may happen with the corpuscles (white) in malaria: in other words, immature forms of these elements may be oured out into the blood, in consequence of the infectious process the loss of these being greater. In the case of tertian and quartan fevers, the development of the phagocytic function is in intimate relation to the life cycle of the parasites and to the eveolution of the fever: such has, indeed, been proved by the researches of Golgi. According to him, we shall look in vain in the circulating blood for manifestations of phagocytosis in regard to the malarial parasites when the latter are in their endoglobular stage, and even when they are found in the phase preceding their perfect maturation; on the other hand, we can readily perceive the phenomena of phagocytosis when the parasites have reached maturity, and are about to become segmented or have already divided. They begin with the onset of the attack, are most evident from three to four hours later, and terminate a few hours after the end of the attack, but even later there are events which seem to represent the continuation of the process; the phenomena, in their entirety, occur in a period of from six to eight or twelve hours. He describes as existent in the blood, during the period of development of the attack, white corpuscles containing bodies in process of

segmentation,or with well-formed spores,or isolated masses of pigment.Later,there are in the blood leucocytes containing the same malarial bodies in a more advanced stage of disaggregation.The destruction of matter is accomplished after ten or twelve hours;and in the next attack these phagocytes which now disappear undergo the same changes.The follwwing law is formulated by Golgi on these facts:"Pgagocytosis is a process which develops periodically like a regular function of the white cells,a function which develops in a certain manner corresponding to determined phases in the evolutionary cycle of the malarial parasite and in a certain period of each febrile attack".From what has already been said,it is evident that phagocytosis occurs throughout the vascular system,but preferably in certain viscera, such as the liver,spleen,etc.;for which reason what is seen in an examination of blood from the finger should be regarded as a mere episode in this process which,at least in this group of fevers,is chiefly carried on in the internal organs,so that we are unable to state that the process is not taking place elsewhere is we do not find examples of phagocytosis in the peripheral blood. The phagocytic bodies,especially the leucocytes including the round masses of pigment found at the centre of fission forms,in summer tertian fever begin to appear at the onset of the attack,and durin the attack they usually increase in number until towards its close they become exceedingly numerous.In typical cases of aestival tertain,the largest number of pigmented white bloodcells is usually seen at about the time of the precritical elevation of temperature.During the brief period of apyrexia,the phagocytes diminish to a notable extent;and in rare cases they disappear,and at the beginning of the next seizure they are seen to be more numerous.In almost every cases one can prove these occurrences:indeed there are some cases of mild aestival tertian fever in which for a short time no parasites can be found in the peripheral blood,but in which the presence of pigmented leucocytes allows of an accurate diagnosis of the disease.In cases of infection of recent date,one may easily follow this cyclic function of the white corpuscles,which is accomplished in correspondence to the febrile attacks;but it is not seen in cases in which the malarial infection has lasted for some time.The brevity of the periods of apyrexia increases the difficulty of deciding when the leucocytes, which are found in these cases always,increase or diminish.It is not difficult to explain why in these cases phagocytes should be found in the blood not only during and shortly after the febrile attack,but also during the whole period of apyrexia.It is well known that when the acute infection ceases,the phagocytes slowly leave the general vascular system of the viscera,lungs, intestines,kidneys,etc.,and collect in the spleen,liver, and bone-marrow.Now,experience has shown that this purification of the circulation takes for its completion many hours and in some cases several days,according to the gravity of the parasitic invasion:we can therefore understand that during the period of apyrexia interposed between two attacks we should continue to see phagocytes circulating in the blood,when because of

a succession of febrile attacks numbers of them have polluted the capillary system of the viscera.The presence of the pigmented leucocytes in scanty number in the blood for several days,- five or six after the parasites have disappeared,- in the apyrexia between a series of relapses,can be accounted for in the same way.As a rule,the phagocytes are exceedingly numerous in the majority of pernicious-fever cases.We are more liable to find in these grave infections than in the ordinary aestival tertian,in addition to the pigmented leucocytes,phagocytes contaning complete sporulation, and parasite-infected brassy bodies,pigmented and globuliferous endothelial cells,etc.The presence of the large macrophagi,which have been already described,and some of which show degenerations,as the most striking feature of these cases.For five,six,or eight days after a cure with quinine,we generally see phagocytes circulating in the blood.If the parasites and phagocytes were numerous in the blood before the exhibition of the remedy,after the fever has been cured by the quinine the pigmented leucocytes ate seen in the circulation for a variable time,even for days.During the action of the drug,we often are able to perceive an increase in the number of the pigmented and globuliferous leucocytes - the reason for which is found in the fact that the phagocytes seize all the parasitic bodies,the development of which has been arrested by the quinine;and that,moreover, the trnsformation of the red corpuscles into brassy bodies is favoured by the medicament itself - whence there is an increase in the amount of material which the phagocytes might seize.It is more perfectly in pernicious fevers than in ordinary infections, and,what is worthy of note, not only in pernicious fevers which are detined to recover,but in those which have a fatal ending, that this incfease in phagocytosis after the administration of quinine is observed.No constant results are forthcoming from a careful examination of the blood in cases in which a spontaneous cure has occurred. Sometimes,when the attacks have become weaker and finally disappeared,one may see an increase in the number of phagocytes as compared with that seen in the days preceding those in which the infection tended to become spent:on the contrary,the diminution of pigmented leucocytes appears to keep pace with the disappearance of the parasites in other cases.When there is a persistence of crescent bodies in the blood after the cessation of the fever,we continue to see pigmented leucocytes at intervals,just so long as the crescent bodies are present;not infrequently we also see included round bodies with pigment in wreath form,or true crescents.The fact that in these cases the pigment contained within the leucocytes is in fine needles or rods,so that we can be sure that it has come fron degenerated and included crescents,is particularly noteworthy.We also see that,on comparison of these facts with those observed in quartan and tertian fevers,even in aestivo-autumnal fevers,the most intense phagocytosis corresponds to the period in which the parasites are multiplying.But there are some differences,which are indicated by what has been said above.In the first place,in grave fevers we often find globuliferous cells,and especially macrophagi, containing parasite-infected brassy bodies.The included

red corpuscles may be entirely decolourised, or may appear almost normal; they may contain young non-pigmented plasmodia, or pigmented forms, or small bodies with central pigment in fission, or bodies of the crescent stage. Consequently, the parasites, even when they are in the phase preceding their full development, and also when they are endoglobular, may in grave fevers present the process of phagocytosis. It appears certain that the special modifications which the parasite-infected red corpuscles may undergo in this kind of fever partly explain their inclusion within the leucocytes, an inclusion which may occur even when much of the parasite-infected globule survives. The tertian and quartan parasites, as we have seen, do not present in their corresponding stages these changes; and in them, also, in the case of grave fevers, we note with less distinctness periodicity of phagocytosis. The reason for this difference is found in the shortness of the periods of apyrexia in aestival fevers, the fact that in these fevers the multiplication of the parasites from which is derived the greater part of the substances taken up by the phagocytes occurs chiefly, if not exclusively, in the internal viscera, and, finally, in the greater tendency towards an irregular clinical course of these affections. It is apparent, then, that in malarial fever phagocytosis is of great importance. But, if we attempt to ascertain which part phagocytosis takes in the defence of the organism against the parasitic invasion, what influence it exerts upon the course of the infection, and if to it is due spontaneous recovery, we come against many difficulties in the interpretation and comprehension of the facts. For this reason it is not to be wondered at that the reports of various investigators do not agree. Some accord to phagocytosis a secondary place, while others hold that it is mainly responsible for the defence of the organism and the production of immunity in malaria. Nevertheless, the function which belongs to the phagocytes of clearing the vascular system from the detritus and dead corpuscles, deposited during acute infections, is a fact beyond doubt. When we think of the large amount of black pigment that is set free in all parts of the vascular system in some pernicious fevers, and of the great number of degenerated red corpuscles and of free parasites which become included in endothelial cells and in leucocytes, and recall the fact that all these matters are deposited in certain viscera, the spleen and liver chiefly, in the course of a few days, we are able to realise the importance of the function. In a relatively short space of time, the vascular system of the most important viscera - as, for instance, the brain - is restored to conditions essential to a normal circulation of the blood. We may add that the return to a normal condition of the spleen, liver, and bone-marrow, in which the débris of the infection is deposited and remains for a while, is in part the result of a series of phagocytic processes, which are accomplished slowly and in regular succession. In the course of acute infections there occur, in certain organs, degenerative changes in the cells of the parenchyma, and even more or less extensive necrosis of the tissue, this having been observed chiefly in the spleen

and liver.In the case of the liver,where the process can be clearly observed,Bignami has shown that these necrosed areas are eliminated and replaced by a tissue of neoformation,which originates in the special cells of the organ itself only when the whole vascular system of the necrotic area has been freed and cleansed from the foreign bodies deposited therein.The cleansing of the pigment and of the foreign bodies deposited during an acute infection occurs more rapidly in the bone-marrow than in any other organ.Indeed,as Bignami noted in sections from cadavers of persons dying at varying periods after the cessation of the infection,we find that the marrow contains a scanty amount of black pigment,or scarcely any in cases in which the melanosis of the spleen and liver is still intense.Now,this return to the normal,which cannot help having a beneficial action upon the activity of the bone-marrow as a haemopoietic organ,is ultimately the work of the phagocytes. By reason of the return to the normal condition of the tissues affected through their agency,we find their importance to be great - even limiting the function of the phagocytes to that of spodoferous and spodophagous cells.The question as to whether the pernicious infections are such because of deficient phagocytosis, and the mild infections mild by reason of the energy of this process,has been much debated.In his researches into quartan and tertian fevers,Golgi was led to attribute an importance to phagocytosis from this standpoint which is not generally admitted.He noticed that during each febrile attack the leucocytes contained not only the retrogression products of the parasites,but also a certain number of parasites themselves.If this were not the case,and if all the parasites invariably completed their life cycle,then,according to him,every case of intermittent malarial fever would go on increasing in severity even to the point of transformation into pernicious fever,which,as we all know,is not the case. Indeed,it cannot be admitted from actual observation that phagocytosis is the only factor in preventing the aggravation of all cases of fever,and especially the conversion of quartan and tertian into pernicious forms. In fact,from the time that the parasites of quartan and tertian infections have been known there have been no examples of perhicious fever caused by them.This,as we have observed elsewhere,leads one to attribute this constant fact to the biological properties of this group of parasites,and not to functions of defence and individual reactions which are so apt to be variable in their action.The virulence and toxicity of the parasites in this group are especially productive of pernicious fevers,which are caused only by ghe parasites of the aestivo-autumnal variety.The part played by phagocytosis in spontaneous recovery from the disease has been subjected to much disputation.In the case of grave infections it is not true that some of them become fatal because of insufficinet phagocytosis,and that others are cured from the efficacy of this defensive process.A close examination of the facts shows that there are fatal pernicious fevers with extensive phagocytosis,and others in which the process is feeble;the

first occur usually in relapses of malaria, the second in primary infections. As a rule, however, phagocytosis is very active in grave infections, so much so that up to a certain point we may consider the number of phagocytes to be in proportion to the number of parasites: in other words, phagocytosis is most active when there is the greatest number of parasitic forms in the condition necessary to admit of their being taken up and included, as has been already described. This condition of things warrants the belief that the result of these infective diseases is in part dependent upon the primary number of parasites, and is in part under the control of a complex series of factors which in their entirety constitute what is known as the power of resistance of the organism. It is generally thought that it is the unjustifiable simplification of a very complex process to attenpt to explain the resistance and relative immunity, acquired by many patients with malaria during the course of an infection, by phagocytosis alone.

KIDNEYS.

In chronic malaria these organs do not, as a rule, show any great changes. The congestive and the atrophic are the two forms of kidneys described. The former, the engorged kidneys, are of large size and increased in weight; the surface is smooth, the consistency firm, and the colour of a deep red. The congestion is especially marked in the pyramids. All the vessels are distended, and the congestion is sometimes so extreme that the interstitial haemorrhages may result, or haemorrhages into the interior of the tubules. The epithelium of the latter is gramular; there is often desquamation, and the presence of hyaline casts may be noted. On the other hand, the atrophic kidneys are small, and irregular in outline. The capsule is adherent, the consistency oncreased. The kidneys show a maroon or mahigany colour, or a blotchy appearance. Small cysts are often to be found. Both the epithelium and the connective tissue of the tubules show alterations. Chronic malaria is sometimes followed by amyloid degeneration. This has been noted in the kidneys by Laveran (Traité des Fièvres palustres, p.94) in two instances, but in both of them the malarial cachexia was complicated by chronic broncho-pneumonia and bronchiectasis. Frerichs (Lehrbuch der Leberkrankheiten) describes three cases, while Marchiafava and Bignami (Riforma Medica, 1891, i., p.571) have carefully studied several instances. The distribution of the amyloid substance in their cases was as follows: The degeneration was most prevalent in the kidneys, where not only the vessels of small and medium size and glomeruli were affected, but also, to a considerable extent, the walls of the renal tubules. Of a very grave character are the degenerations of the renal parenchyma and the alteration of the interstitial tissue. Next to the renal organs, the amyloid degeneration is most severe in the intestines and the spleen. In the intestine the degeneration affects chiefly the vessels of the villi, but also the vessels of the submucosa, and to a less extent those of the other intestinal coats. In the spleen the vascular network of the periphery of the follicles is particularly affected. Here one sees usually the deposition of great blocks of amyloid substance, while in the trabeculae of the pulp the process is in its beginning or is entirely wanting. In the liver there is a less extensive and diffuse deposition of amyloid substance than in the

kidneys.The degeneration affects islands of hepatic tissue which are irregularly disseminated;so that,for example,one may see an island of the size of a lobule, or larger,from which hepatic tissue has entirely disappeared,the vascular network showing that there is a most grave amyloid degeneration,while about this the hepatic tissue has a normal appearance.The alteration in question spreads from the periphery of the hepatic lobules,where the small areas of degeneration are first to be observed.

MALARIAL CIRRHOSIS.

With malarial fever there used to be associated hepatic cirrhosis,chronic renal lesions,and,in some instances,chronic inflammation of the lungs,endocardium,and central nervous system.Indeed,in almost all works upon medicine,malarial fever is included as one of the etiological factors in ordinary atrophic cirrhosis of the liver.This statement has been based almost entirely upon rough clinical observation,no one having definitely traced the development of the cirrhosis from changes following acute or chronic malaria.Frerichs (loc.cit.) noted the rarity of cirrhosis in patients dying with chronic malaria,though in five instances this was the only etiological cause which he could discover.Laveran (loc.cit.,p.90) in his considerable experience has seen but two cases of atrophic cirrhosis following malarial fever,and Welch only one instance of this.Two forms of chronic malarial cirrhosis and three of chronic malarial hepatitis are recognised by Kelsch and Kiéner,who describe them at length,namely, Insular cirrhosis with nodular hepatitis and insular cirrhosis with diffuse parenchymatous hepatitis;and annular cirrhosis with nodular or diffuse parenchymatous hepatitis.The general appearance of the liver is that of ordinary atrophic cirrhosis in these cases. The development of ordinary chronic hepatic tumour in malarial cachexia is described by Bignami,who concludes that there is little evidence to show that ordinary atrophic cirrhosis is a frequent follower of the disease,and remarks that it is easy to understand from this that it is"not difficult to make a differential diagnosis between this form of chronic tumour - or of chronic hepatitis,as one might say - from the other forms of cirrhosis"There are not facts or reasons sufficient to cause us to believe that ordinary cirrhosis can follow a chronic tumour.The structure in the two cases is absolutely different.In the one we have an extensive new formation of connective tissue,multilobular in nature,retracting about the included lobules; in the other,a more scanty formation of perilobular connective tissue about a single lobule,not contracting, together with grave alterations of the lobules themselves,especially of their vascular and lymphatic system,not depending,as we have seen,upon the new formation of perilobular connective tissue,but due to lesions primarily local.Atrophic conditions of the liver exist in malaria,but are simple atrophies,and occur in patients who are exhausted,for example,by profuse diarrhoea, etc.,or in cases of progressive post-malarial anaemia. The complete want,or almost complete absence,of any process tending toward regeneration,resulting from

grave and diffuse retrogressive lesions,may be taken as responsible for their occurrence.The fact that many conditions exist in the organs in malarial fever,which might well be the starting-point for extensive growth of connective tissue,has been emphasised by Barker (Johns Hopkins Hosp,Reps.,Vol.v.),who at the same time discusses the relation of malarial infections to the cirrhotic process.The development of characteristic cirrhosis of the liver and of the kidneys in rabbits, following focal necrosis not dissimilar to those found in the liver in acute malarial onfections,has been observed by Flexner (Med.News,Aug.,1894) after the injection of blood-serum from one animal into another. Though the possibility of its occurrence cannot be denied,the question of the possibility of the development of a true cirrhotic atrophy of the liver,of malarial origin,is not settled;the development has never been actually traced,and the condition,if it exists at all,is probably rare.

S Y M P T O M A T O L O G Y.

INCUBATION.

The duration of the period of incubation of malarial fever has been variously described by those who have given the question special study. It has undoubtedly been observed that characteristic malarial fever may appear very shortly after exposure in a malarious district, many observers believing that this may occur within a shorter time than twenty-four hours. It is possible that the febrile attacks which may occur sometimes immediately after exposure at night in damp, marshy, malarious districts may have some other cause than malarial infection. Thus, Plehn describes cases where, after exposure at night in very malarious districts in West Africa, there was an immediate paroxysm similar to a malarial attack, which, however, did not recur until the appearance, ten days later, of a true malarial fever, which doubtless dated its infection from the night of exposure. At the time of the first paroxysm the blood was negative, the parasite (aestivo-autumnal) not appearing until ten days later. The hypothesis of Plehn, that the initial paroxysm was due to the absorption of some toxic substance produced - perhaps by the parasite outside of the body - seems a little far-fetched. More commonly an interval of one or two weeks may be made out between the time of exposure and the time of the breaking out of the disease. Hertz (Ziemssen's Ency., Vol. ii., p. 588) states that the period of incubation is commonly reckoned at from six to twenty days, but believes that the disease may appear immediately after the entrance of the virus into the system. Maillot (Treatise on Fevers, p. 263) considered the mean period of incubation to be from ten to twelve days; while Sorel (Arch. de Méd. milit., 1884, T. 3, p. 273) estimated it at from seven to nine days. A perusal of the literature of the disease will show that many exceedingly long periods of incubation have from time to time been reported, though many of them ar open to considerable doubt. Such, for instance, is the case of Blaxall (Cited by Hertz., loc. cit.), where, after spending five days in the harbour of Port Louis, two of the crew of a man-of-war were attacked, at the end of, respectively, twelve and fourteen days, with quotidian intermittent fever, while two others developed tertain fever at the end of, respectively, forty-eight and one hundred and eighty-four days after embarcation. In view of our present knowledge, it is probable that many cases of prolonged incubation represent relapses of earlier attacks, the manifestations of which have been present and would have been recognised had the patients been properly observed by those who had to come in contact with them. The question has been studied in a more intelligent manner of recent years since the discovery of the germ of the disease, and the inoculation experiments of Gerhardt, Mariotti and Ciarrochi, Marchiafava and Celli, Gualdi and Antolisei, Angelini, Di Mattei, Calandruccio, Bein, Bacelli, and Sacharov. The period of incubation in these cases, where the blood of one malarial patient was introduced intravenously or hypodermically into a

healthy individual, have varied greatly. In individual cases there was a variance in the period of incubation of from six to eighteen days, while the average duration was from eleven to twelve days. More recently, Bastianelli and Bignami have contributed four new cases to this list, and have given the subject their careful attention. The period of incubation in their cases of artificial inoculation represents the time necessary for the inoculated parasites to arrive, by multiplication, at the quantity necessary to determine the fever. The period of incubation, with a given variety of parasites, varies inversely to the quantity of material inoculated. The mean and minimum period of incubation, under equal conditions, varies with the various groups of the fever; it is least with aestival fevers, a little longer with tertian fever, and yet longer with quartan fever. They believe that they are justified in concluding that the period of incubation in experimental malarial infections is not a constant quantity, but varies in the same group of fevers and in different groups. In a given group of fevers it depends primarily upon the quantity of material inoculated. They say that in different groups of fevers it varies with the special capacity for reproduction of the parasitic variety and with the rapidity of the cycle of development of the parasite of the disease. After analysing their cases, they conclude that in quartan fever the maximum duration of the period is fifteen days, the minimum eleven, and the mean thirteen; in tertian fever, the maximum twelve, the minimum six, and the mean ten; whereas in aestivo-autumnal fever the maximum is five, the minimum two and the mean three days. We may take it, then that the incubation period in aestivo-autumnal fever may be as brief as two days; and this fact is well worth noting. As we do not know how or in what form it occurs, we cannot positively assume that these figures represent the period of incubation in infection as it ordinarily occurs. It is striking to see how well their conclusions agree with the deductions which have been drawn by other observers before the discovery of the malarial parasite. It is with the aestivo-autumnal variety of the parasite, that variety that is associated with the pernicious fevers, that the short periods of incubation have been observed, while the older clinical observations of short periods of incubation relate to the same class of cases. The facts of clinical observation agree quite closely with the general results of inoculations in tertian and quartan fevers, while the demonstration that the disease may appear in forty-eight hours after small intravenous inoculations makes us believe that the true incibation period may be extremely short in some very malignant fevers, however the infection may take place. To account for certain early manifestations of the fever Plehn (Virchow's Arch., 1892, cxxix, 285) propounds a very ingenious theory. As already mentioned, he asserts that he has noticed in several instances a well-marked febrile reaction occurring within a few hours after exposure in malarious districts, and simulating a single malarial paroxysm. The examination of the blood was negative. From nine to twelve days later, however, characteristic malarial fever developed, the parasites being readily found in the

blood.He suggests that by exposure in extremely malarious districts the individual may absorb a sufficient quantity of a pyrogenic toxin to cause immediately a single paroxysm days before the true incubation period has been passed through.This theory,however,is not generally entertained.We may take it,then,that,basing our conclusions upon the comparison between clinical deductions and the accurate observation of inoculation experiments,it seems likely that the ordinary period of incubation in tertian fever is about ten or twelve days, in quartan fever a little longer,while in aestivo-autumnal fever the period in question probably averages a somewhat longer time than in both these varieties of the disease,ranging from twenty-four hours,or even less,to ten days or two weeks.

Classification.

There are two principal groups of malarial fevers - viz., first,the regular intermittent fevers,occurring throughout the malarial season;and,second,the more irregular,often more or less continued fevers,occurring at only the height of the malarial season,the late summer and autumn,and in temperate climates.Nevertheless,one may separate three distinct types of fever under these main classes,depending in turn upon infection with one of the three types of the malarial parasite which have already been described.Thus,the first class,the regular intermittent fevers,includes (a) tertian fever,with its combinations (double tertian fever),and (b) quartan fever,with its combinations (double and triple quartan fever).The second class of fevers,that including the more irregular varieties,occurring as it does at the height of the malarial season (August,September,October), justly deserves the name (c) aestivo-autumnal fever, which the Italian physicians gave to it long ago;it depends upon infection with the third variety of the malarial parasite previously described.Almost all malarious localities furnish instances of tertian fever. The quartan variety,however,is rare in many districts where the other forms of infection are frequent.There are certain regions,however,- such as in certain parts of Sicily and in the neighbourhood of Pavia in Italy,- in which quartan fever is particularly common.In the United States of America it appears to be rare:thus, out of nearly a thousand cases observed at the Johns Hopkins Hospital,only nine cases of quartan fever have been observed.Wherever they exist,these types of the disease are the same.The milder forms - tertian and quartan fever - alone prevail in districts where malaria is very uncommon.In tropical countries the severer types of aestivo-autumnal fevers are in excess.As one passes aways from the equator,only the milder tertian and quartan fevers are to be seen in the earlier part of the malarial season,while the aestivo-autumnal fevers appear in the later summer and early autumn.

TERTAIN FEVER.

This form of malarial fever admits of two varieties - viz.,single infections or tertian intermittent fever, and double infections or quotidian intermittent fever.

Single infections - Tertian Intermittent Fever.

Infection with the tertian parasite is responsible for this type of malarial fever.This organism has already been described,and possesses the remarkable characteristic of existing in the blood of the infected

individual in great groups, all the members of which are approximately at the same stage of development, and pass through their cycle of life together, all the organisms composing this group undergoing segmentation within a period of several hours; it requires, as has been said, approximately forty-eight hours to complete its cycle of development. In infections, then, with a single group of parasites segmentation occurs at intervals appromimately forty-eight hours apart. As Golgi so clearly showed, the febrile paroxysm is always associated with the segmentation of a group of malarial parasites, and, as one might expect, the chief characteristic of this type of fever consists in intermittent febrile paroxysms occurring every other day. The regularity with which these paroxysms recur is truly remarkable, the onset sometimes taking place at almost exactly the same hour day after day. More frequently there are slight differences, generally, however, of more than two hours, between the time at which succeeding paroxysms recur. Slight anticipation in the hour of onset is more common than retardation in the opinion of most observers.

Clinical Course.

The chill, the fever, and the defervescence are the three well-known stages into which the paroxysm of this type of malaria is divided.

There may be no premonitory symptoms to usher in the chill. More commonly, however, for a period of from a few minutes to half an hour, the patient complains of uneasy sensations - a slight headache, or perhaps a little giddiness or fatigue. Not infrequently the onset is preceded by yawning. If the temperature is carefully noted during this period, it will usually be found that a slight elevation has already begun to appear. Immediately after this, the patient begins to complain of chilly sensations, usually up and down the back; these increase, the patient begins to shiver, and soon a general shaking chill follows. The chill is often extremely violent: the teeth chatter; the whole body is thrown into so violent a tremor that the bed and often surrounding objects in the room are shaken. The skin is pale, or often somewhat cyanotic and cool, though wholly disproportionately so in comparison to the intense feeling of cold complained of by the patient. It is often moist, while the erection of the hair follicles gives rise to the characteristic cutis anserina or "goose skin". The pupils are usually dilated. The patient complains of headache, buzzing in the ears, vertigo, and sometimes of viscual disturbances. The pulse is small and rapid, and often of rather high tension. There may be nausea and vomiting. The duration of the chill varies materially in different cases: it may last as long as an hour, though usually the period is considerably shorter - from ten minutes to half an hour. Not infrequently no actual shaking occurs, the patient complaining only of chilly sensations. Occasionally, though very rarely in this type of fever, the chill may be entirely absent. During this period of the chill the temperature of the patient rises rapidly, and, at the end of the chilly sensations, may have reached almost its height. Within two hours after the onset of the paroxysm, as a rule, almost the maximum point of pyrexia is attained.

The febrile or pyrexial stage is the next to appear. The chilly sensations, after a certain length of time,

become less marked and are interrupted by flushes of heat, which become more frequent, and finally wholly replace the chill. Then begins the second or febrile stage of the paroxysm. The patient complains of an intense burning heat; the skin is flushed, hot, and dry, the conjunctivae injected, the pulse becomes fuller, but remains rapid: it may be dicrotic. The patient complains bitterly of headache, and often of vertigo and buzzing in the ears. The coverings of his bed, for which but a short time ago he had begged, are now thrown aside. Often there is intense thirst. The patient is frequently restless, throwing himself from one side of the bed to another. In some instances there is active delirium. It has been known for a patient to jump out of the window of the ward or house during the febrile stage of a double tertian paroxysm, and be killed by the fall. In other instances the patient is dull, drowsy, and typhoidal in appearance, complaining upon inquiry only of intense headache and aching pains in the back and extremities. In certain cases there may be epistaxis. Sometimes vomiting and diarrhoea are observed. Not infrequently there is a slight cough. The patient's face is flushed, the conjunctivae are injected, and the tongue is often dry and coated. There is often a dusky, yellowish-gray colour of the skin, while the lips and mucous membranes are pale. Herpes on the lips and nose is very common. Various cutaneous eruptions have been noted, usually erythematous in nature. In several instances an extensive general urticaria has been observed. The respiration is not particularly accelerated, though the pulse is often rapid and somewhat dicrotic. The lungs are generally clear on auscultation and percussion, though, not infrequently, evidences of a general bronchitis - sonorous and sibilant râles - mat be heard throughout the chest, more frequently in the back. The heart sounds are usually clear, though a soft systolic murmur may be heard over the body of the heart. The abdomen is usually natural in appearance. The area of hepatic dulness is often somewhat increased. There is frequently tenderness on pressure in the region of the spleen, while the area of the splenic dulness is almost invariably increased. In most cases the spleen is easily palpable. In fresh cases the border is rounded and soft; in older cases, where there have been numerous previous attacks, the border is often sharp and firm, reaching sometimes a considerable distance below the costal margin. The splenic tumour is particularly striking in children. The most marked splenic enlargements occur, however, in the cases which show the more irregular aestivo-autumnal fevers. Massuriany (St. Petersb. med. Woch., 1884) noted the presence of a soft souffle over the splenic area, which Bouchard has compared to a uterine bruit. The duration of the febrile period is usually four or five hours, though, not infrequently, considerably longer; and during it the temperature reaches its maximum height, thermometric registrations of as high as 108° F. having been observed.

The third or sweating stage of the paroxysm usually follows quite suddenly after the stage of pyrexia has existed for four or five hours. The patient begins to feel relief from the sensation of oppressive heat from which he had been suffering, and then, quite suddenly,

breaks into a profuse sweat. The sweating is often excessive; the night-clothes and bedding may be soaked. In association with this the temperature falls, usually quite rapidly. The pulse, which has been rapid, becomes slow and full, and the patient often passes into a refreshing sleep. The temperature falls, almost invariably, to a subnormal point. The defervescence is generally somewhat longer than the rise of temperature, though it may be very short and sudden; it commonly lasts from two to four hours, though often longer than this. The duration of the sweating stage varies considerably. About eleven hours would represent the average length of the entire paroxysm from the time the temperature passed 99° F. until it reached this point again.

The paroxysms occur more frequently during the day than during the night, the onset perhaps being more commonly noted between midnight and noon, though it may occur at any hour of the day or night: indeed, it is not at all uncommon to find paroxysms beginning in the afternoon. The paroxysm in children is not the same as that seen in adults. Very commonly in young children both the first and the third stages, the chill and the sweating, may be absent or abortive. The first stage is then generally represented by a slight restlessness. The face looks pinched, the eyes are sunken; the finger-tips and toes become cyanotic and cold, while the child may yawn and stretch itself. Nausea, vomiting, and diarrhoea are particularly common. These may be the only manifestations of the first stage. Commonly, however, these symptoms are followed by grave nervous phenomena. The chill in malaria, as in other acute diseases, is not infrequently represented in the young child by general convulsions. These begin usually with a slight spasmodic twitching of the eyelids or of the extremities, the spasm soon becoming general. The first and third stage of the paroxysm may be entirely lacking in many instances, leaving out of account a slight coldness of the hands and blueness of the finger-tips, as well as a somewhat pinched expression of the countenance in the first stage.

The patient often feels quite well during the period of intermission, so much so that it is not uncommon for patients to pass through a number of paroxysms before calling in a physician, believing after each that the disease is at an end. The temperature after the sweating stage becomes almost invariably subnormal, and often remains so during the greater part of the next day. About forty-eight hours after the onset of the first paroxysm, the fresh group of parasites proceeding from the segmentation of two days before having reached maturity and entered again upon segmentation, a fresh paroxysm begins. Slight anticipatory paroxysms are very common, more so than retardation. Often, as has been said, the time of onset of several successive paroxysms is almost exactly the same. More commonly, though, there are slight variations of an hour or two, anticipation or retardation. In these instances the parasite passes its cycle of existence through a little quicker or a little slower than in the typical forty-eight hours.

The condition of the blood in this variety of malarial fever has already been fully considered.

Double Infections - Quotidian Intermittent Fever.

Among the mildest forms of malarial fever to be observed in temperate climates are the single tertian infections;more commonly the individual shows an infection with two groups of the tertian parasite.These groups reach maturity on alternate days.Segmentation,then,of a group of parasites occurs every day,and,as one might expect,daily paroxysms,quotidian intermittent fever, results therefrom.The paroxysms in these instances are similar in every way to those of single tertian infections.The manner of onset and the duration are the same, while during the periods of intermission the temperature is likewise always subnormal.It is common,however, for the paroxysms on successive days to show slight constant differences in their hours of onset,one group of parasites arriving at maturity at an hour slightly different from that of the other.These differences are usually not great,though they may be considerable,one paroxysm beginning in the morning,that upon the following day in the afternoon.Very commonly one set of organisms is more numerous than the other,causing thus a more severe paroxysm.The chart then shows alternate mild and severe attacks.Even without the confirmation obtained by submitting the blood to a special examination,these facts alone might lead to the recognition of the dependence of this quotidian fever upon a double infection.

The condition of the blood has already been fully described elsewhere.

QUARTAN FEVER.

There are three types of quartan fever requiring description - viz., single infections or quartan intermittent fever, double infections or double quartan intermittent fever,and triple infections or quotidian (triple quartan) intermittent fever.

Single Infections - Quartan Intermittent Fever.

This form of malarial fever is due to the presence in the blood of the quartan parasite,an organism which, just as in the case of the tertian parasite,possesses the remarkable characteristic of existing in the blood in great groups,all the members of which are,approximately,at the same stage of development.The cycle of development of the quartan parasite lasts approximately seventy-two hours,segmentation occurring every fourth day.The characteristics,then,of single quartan infections are quartan intermittent paroxysms,two days of complete intermission existing between.The paroxysm in quartan fever resembles in all its features that observed in tertian infection.The duration in these cases averages between ten and eleven hours.The same periods of subnormal temperature,lasting often during the greater part of the two days of intermission,are observed. A tendency towards anticipation or retardation in the paroxysms is less often noted than in tertian infection; and the regularity of the paroxysms in quartan infection is the most remarkable characteristic of the disease.

The condition of the blood has already been noted.

Double Infections - Double Quartan Fever.

There may often be present in the blood at the same time more than one group of quartan parasites.When two groups are present,segmentation usually occurs on two successive days,with a day of intermission

following.Clinically,therefore,these double infections are characterised by chills upon two successive days, with a day of complete intermission following.The examination of the blood shows the presence of two groups of the quartan parasite;and the paroxysms in these instances ate exactly similar to those observed in single infection.

Triple Infections - Triple Quartan Fever.

It is no unusual experience to find three groups of the quartan parasite present in the blood at the same time.These groups reach maturity on successive days,and cause,therefore,quatidian intermittent fever. The symptoms of quotidian fever depending upon a triple quartan infection differ often in no wise from those depending upon a double tertian infection;and examination of the blood shows in these instances the presence,in different stages of development,of three groups of the quartan parasite.Daily paroxysms,exactly similar in nature,occur in both instances.The same period of subnormal temperature may be noted,and the diagnosis,without examination of the blood,may be impossible.

AESTIVO-AUTUMNAL FEVER.

The aestivo-autumnal is a type of fever that differs materially from the regular intermittent fevers of the early part of the malarial season.It depends upon the presence in the blood of the smaller organism first described by Marchiafava and Celli,the aestivo-autumnal parasite.This organism possesses to a much less marked degree the characteristic of existing in large sharply defined groups,while the length of the cycle of existence appears to vary considerably.At the beginning of many infections an arrangement of groups may,however,be made out,and this arrangement may exist for a certain length of time.Usually,however,before the process has lasted very long,organisms in different stages of development may be found at any time during the fever.In some instances groups of parasites,with a cycle lasting about twenty-four hours,have apparently been made out,while in others distinct groups appear to pass through a cycle lasting considerably longer,as long as forty-eight hours or even more.There are very varied forms of aestivo-autumnal to be met with in practice.Quotidian intermittent fever is not at all an infrequent form.Here the paroxysms may resemble very closely those of tertian or quartan fever,and in some instances,without the examination of the blood,the distinction from double tertian or triple quartan infections cannot be made.In these instances the process begins with a sharp chill,and ends with a marked sweating stage,the duration of the paroxysm being perhaps exactly similar to that in the regularly intermittent fevers.More commonly,however,the paroxysms are longer and more drawn out,lasting perhaps, as long as twenty hours.Here the first stage often differs greatly from that in tertian or quartan fever. While in the regularly intermittent fevers the onset is rapid and usually associated with a chill,in these instances the rise may be much more gradual,while the chill is not infrequently altogether lacking.Often a slight transient chill may be observed some time after the beginning of the rise in temperature.The chill in aestivo-autumnal fever can by no means be called the

initial symptom in the paroxysm; the fever has often become well-marked before the onset of the rigor. Usually, after a certain number of paroxysms, a distinct irregularity in the fever becomes evident. Either from the lengthening out of one of the paroxysms or from the anticipation of the following paroxysm, the intermissions between the two becomes, perhaps, completely obliterated or indicated only by a slight drop in the temperature, until there results an irregular continued fever in which there is no trace of the paroxysm.

Recurrence of the early paroxysms at greater intervals, than one from the other, is not infrequently observed. These intervals are frequently forty-eight hours, more or less ("Aestivo-autumnal tertian fever; malignant tertian fever" - Marchiafava and Bignami). In these instances the paroxysms are usually particularly long, lasting sometimes as much as thirty-six hours. The very gradual rise in temperature, which is often unaccompanied by a chill, and the slow fall, are in striking contrast to the chart of an ordinary tertian fever. The authors cited in parenthesis above, who believe that they can distinguish two separate types of the aestivo-autumnal parasite, the quotidian and the tertian, have described minutely the fever curve in these cases with longer intervals. This class of cases they term "malignant tertian fever", in contradistinction to the milder regularly intermittent tertian fever. They describe what they believe to be a characteristic fever curve, the more or less sudden onset of the symptoms, a pseudo-crisis, a pre-critical elevation of temperature, which often reaches a point higher than has been previously attained, and, finally, the actual crisis. Charts similar to this have been observed by others, and reproduced in various publications, though they have not seen a sufficient number of instances to justify them in believing that such a curve is characteristic of a particular, separate type of parasite. It is certainly true, however, that irregular oscillations in the curve of the fever produced by these parasites are very common. The periods of intermission between paroxysms show, however, usually, a subnormal temperature. As may be readily understood on consideration of the length of the paroxysm - lasting, as it often does, thirty-six hours or more - the periods of apyrexia are, however, very brief.

The irregularity in the hour of onset of the paroxysms is particularly striking in those cases in which the paroxysms occur at intervals of approximately forty-eight hours, one from another. In some cases there is marked retardation, intervals of considerably more than forty-eight hours occurring between the beginning of one paroxysm and that of its successor. More frequently, however, there is anticipation, the paroxysms recurring at intervals of less than forty-eight hours. Now, if, as already stated, the individual paroxysm should last thirty-six hours or more, it may readily be seen how short the period of intermission in these cases would be. Often, then, there is what is termed "malignant remittent fever", in which we have an almost continuous high temperature, with occasional remissions or intermissions lasting, perhaps, less than thirty minutes.

Owing either to an excessive prolongation of the first paroxysm or to an anticipation of the succeeding one, in many instances the new paroxysm begins before the previous one has finished. In these cases the result is, of course, a "continuous" fever. Usually the continuous fevers resulting from aestivo-autumnal infections, though the temperature may never reach the normal point, yet show indications of the paroxysms, and sometimes occasionally abortive chills. In some instances, however, all evidence of paroxysms may be absent, the chart closely simulating that of enteric fever. Such cases are probably often due to infections with more than one group of parasites. The fact that the segmentation of a given group of parasites occurs through an appreciably greater length of time than in regularly intermittent fevers probably accounts for the long duration of some of the paroxysms. So it comes that the chart of aestivo-autumnal fever presents very commonly somewhat the following picture: At the onset there are several intermittent paroxysms occurring at intervals of from twenty-four to forty-eight hours or a little more. After a few of these attacks the fever becomes irregular or continued. As already stated, this may occur through modifications of the curve in the individual paroxysm, or by the same thing in connection with the succession of the the paroxysms. The modifications of the curve that are important are the following: First, the lack of a sharp initial elevation, so that the curve rises in a slow and continuous manner; second, the occurrence of a pseudo-crisis, so that the attack tends to lose its individuality; and, third, the prolongation of the paroxysm, with which an exaggeration of the thermic oscillations during the fastigium is usually associated. The modifications in the succession of the paroxysms may be: First, the reduplication of the attack; second, the anticipation of the paroxysms; third, the retardation of the paroxysms, by which apyrexia is made incomplete; and, fourth, the occurrence of slight oscillations in temperature during the period which ought to be one of apyrexia.

It is a very common thing to find that the case is already one of remittent or continued fever when it comes under observation. The chills are frequently absent; the patient complains bitterly of headache and general pain in his back and limbs. He is usually dull, drowsy, and pathetic, though there may be marked delirium. The face is flushed, the conjunctivae are injected, the tongue red and coated; there is sordes upon the lips and teeth; the patient remains continually in a condition similar to that described in the febrile stage of the ordinary paroxysm. In these instances it is often absolutely impossible, without examination of the blood, to distinguish the case from one of typhoid fever. One repeatedly sees patients with aestivo-autumnal malaria placed under treatment as cases of typhoid fever, the attention being first drawn to the true condition of things by a sudden fall of the temperature to normal, or by the discovery of the the small amoeboid hylaine parasites within the red corpuscles. Grave cerebral or abdominal symptoms develop, often early in the course of these subcontinuous fevers, which frequently tend to

become pernicious.Careful observation may show that these symptoms are paroxysmal.Delirium,drowsiness, stupor,coma,grave cerebral symptoms,local spasms,general convulsive seizures may occur,or perhaps profuse vomiting or a choleriform diarrhoea with collapse.In fact, in the course of subcontinuous aestivo-autumnal infection, any of the symptoms which will be described under the pernicious fevers may suddenly develop.

The term "malarial remittent fever" has sometimes been applied to these cases of more or less continued fever.They have been specially studied by Bacelli,who recognised their true malarial nature,under the name of "subcontinua typhoidea".The tendency of the regularly intermittent fevers,when left to themselves,is towards spontaneous recovery after a certain number of paroxysms,and,while relapses are common and productive,perhaps,of grave secondary disturbances,- anaemia,nephritis, etc.,- the tendency to become pernicious is rarely observed.This is not true of aestivo-autumnal infections as a class.In many instances,indeed,when placed under hygienic conditions the same tendency towards spontaneous recovery,usually with relapses,is to be observed.Often, however,an untreated infection becomes steadily more aggravated,until,finally,death occurs in the midst of so-called pernicious symptoms.Again,aestivo-autumnal infection may be associated in other cases with but slight rises in temperature;there may be no sharp paroxysms,the patient complaining only of langour,anorexia, headache,and pains in the back and extremities.Such cases probably often pass into the condition known as chronic malarial cachexia;and they may lead to errors in diagnosis,though there is usually,if the case has existed for any length of time,a certain degree of anaemia,with the characteristic sallow hue of the skin, while the spleen is almost always hypertrophied.

PERNICIOUS MALARIAL FEVERS.

The term "pernicious" has been applied to certain very malignant forms of malarial fever.It is quite true that the term "malignant fevers" used by the translators of Marchiafava and Bignami's work (The Parasites of Malarial Fevers,New Syd.Soc.,Lond.,1894) is,in the abstract,better;but the eradication of the word "pernicious" appears to the writer injudicious,as it is so firmly implamted in the general usage.The disease, almost invariably,depends upon infection with the aestivo-autumnal parasite.In temperate climates these pernicious fevers are rare,but in the tropics they are extremely common.The pernicious nature of an attack depends,generally,upon several causes:(1)The great numbers of parasites present,and their capacity for rapid multiplication;(2)the special involvement of certain vital organs by the parasites,which,as has already been pointed out,show a remarkable tendency towards accumulation in certain definite organs,varying in different cases;(3)possibly upon greater or less virulence of the parasite.The latter statement is based upon the assumption that the malarial parasites produce a specific toxic substance.Certain authors thus believe that, in the case of infection with a very malignant parasite, pernicious symptoms may result,while but a small number of parasites are present,particularly if the

chief seat of development of the parasite be localised in a particularly vital spot. This is, however, doubtful. While it is probable that a specific toxic substance may be produced by the parasite, and while there is very good reason to believe that there is a difference between the malignity of the parasites in different instances, yet, in a general way, the severity of the symptoms, as demonstrated long ago by Golgi, appears to depend largely upon the number of parasites present. In a general way it may be definitely stated that pernicious fever never occurs without the presence of a considerable number of parasites, though in the peripheral circulation in some of these instances very few organisms may be discoverable. The conditions through which a malarial infection becomes pernicious are: (1) That the infection be produced by one of the varieties of the aestivo-autumnal parasite. On this condition all today are agreed, though there are exceptions, but rare, to this rule - characteristic comatose pernicious fever having been known to be due to a double tertian infection. (2) The second condition relates to the abundance of the parasites, and it may be states as follows: In pernicious fevers, if one takes into consideration not only the examination of the blood from the finger, but also the condition of the vessels of the various organs, it is a striking fact that, however the distribution of the parasites may vary in individual cases, their total number is always considerable. As regards the distribution, one may make the following distinctions: There exist (1) cases in which the number of the parasites is most abundant, yes enormous, while all the organs are uniformly invaded. These are the most common forms of pernicious fever, and are usually accompanied by coma. There are some cases in this category in which the number of parasites in the blood of the finger, of the spleen, and of the bone-marrow, etc., is enormous, while the number in the brain is scanty; clinically, the absence of cerebral phenomena is noted. (2) Cases in which the number of parasites is absolutely and relatively scanty in the bone-marrow, in the spleen, in the liver, while there may be relatively few in the blood of the finger, yet other organs are crowded with parasites. Among these the following localisations are to be made out: (a) The stomach and intestine are chiefly invaded; in these organs the mature forms of the parasite are usually found; these are the cases of pernicious fever in which, clinicaly, intestinal phenomena are to be observed. (b) The brain and meninges are filled with parasites either in sporulation or in all their stages of development; in such cases it is difficult to find not only the sporulating forms, but even young parasites in the spleen. Clinically, there are cerebral phenomena. Though usually several paroxysms have previously existed, the pernicious symptoms may come on quite early in the course of the infection. Almost the first symptom observed, however, in malarious districts may be of a pernicious character.

Clinical Varieties.

The pernicious fevers present several varieties, all of which merit special description:

ALGID FORM.

In this type of pernicious malaria, after several paroxysms, which are in no way remarkable, the patient

very suddenly passes into a condition of extreme collapse.This does not occur at the beginning of the paroxysm, but at a time when the stage of the fever should exist. The temperature may be but slightly elevated:indeed,in some instances it is subnormal.The condition is not unlike that in Asiatic cholera.The mind is clear,there is little suffering,but extreme collapse.The eyes are sunken;the features drawn and pinched;the face expressionless;the tongue dry;the skin moist and covered with a cold sweat.The patient may be so quiet and uncomplaining that it may be only through an accidental examination of the pulse that the true state of affairs may be discovered.The pulse is very rapid and feeble and thready,almost impalpable,becoming imperceptible at the wrist before death.The abdomen is usually retracted; there is often tenderness on pressure in the region of the spleen which latter is palpable.Physical examination of the thorax is negative excepting for the feeble action of the heart.The second sound at the base may be quite inaudible.The course of the disease is sometimes extremely insidious and fatal.

COMATOSE FORM.

By far the most frequently observed type of pernicious malaria is that accompanied by coma;recovery may result after the gravest symptoms,but the paroxysm is usually followed rapidly by a second,which generally proves fatal,if no treatment is adopted.In the comatose type,in the earlier part of the paroxysm,the patient may be slightly delirious,but he soon becomes drowsy and somnolent,passing finally into a condition of profound coma.Not infrequently,in grave malarious districts,the patient comes for the first time under one's observation while in this condition.He is profoundly unconscious; the respiration is often stertorous,and occasionally of the Cheyne-Stokes type.The pupils may be contracted or dilated,sometimes perhaps unequal.There is often - a not unimportant point - a slight jaundice.Not infrequently there is hiccough;the pulse may be full,slow,and of high tension,though towards the end it is often rapid, irregular,and feeble.Local spasms of certain muscles may occur.Thus,there may be well-marked spasm of the lower facial muscles on one side,which may disappear with the paroxysm.

DELIRIOUS FORM.

Most decided symptoms of a different nature may occur in other cases.Delirium,which may be manical, may be observed.Active delusions and hallucinations are not uncommon,while in some instances tetanic convulsions have been noted.In a number of cases hemiplegia has been associated with the paroxysm,disappearing after the attack.At times distinct symptoms of bulbar paralysis may occur.Post-mortem confirmation of the special localisation of the parasite in certain foci in the medualla can usually be obtained in these cases.

HAEMORRHAGIC FORM.

In certain cases of pernicious malarial fever grave haemorrhages may occur.Thus,there may be punctiform haemorrhages in the skin,the mucous membranesmthe retina, and the brain,and these may be manifested in all pernicious fevers.But there is one one variety in which the

symptom of the greatest gravity and danger consists in these haemorrhages.They are seen not only in the skin, which may be covered with them,but in the mucosa of the nose,the bronchi,the intestines,the stomach,and the genital organs;and they may be so abundant that they cause grave anaemia in a few hours,whence arise loss of strength,a thready pulse,dulness of the sensorium, delirium,and convulsions.At the end of the attack the haemorrhages also cease,but the consequences of their occurrence may be such that recourse to all the known means of treating ordinary acute anaemia may be necessary to avert a catastrophe.Furthermore,the anaemia secondary to this form of pernicious fever is of considerable duration,and is sometimes rebellious for a long period to treatment.Some writers subdivide the haemorrhagic pernicious fevers into various forms, giving each the name of the predominant haemorrhage - e.g.,scorbutic,epistactic,haemoptic,haematemetic, enterorrhagic,metrorrhagic,etc.

DIAPHORETIC FORM.

Many writers have described a diaphoretic or sudoriferous type of paroxysm,in which,during the last stage,the sweating becomes excessive,and the patient passes into a condition of collapse with a thready pulse and cold extremities.The case may end fatally of not energetically treated;for the patient is depressed and groans in anguish,his features are drawn into am expression of painful anxiety,the abdomen is retracted and painful,the tongue red and dry,the pulse thready,and the extremities are cold.

BILIOUS FORM.

The chief symptom of this type of pernicious fever is the vomiting of large quantitiesmof bile-stained fluid.,and this phenomenon is usually accompanied by stools similar to those passed during a bilious attack.

GASTRALGIC AND CARDIALGIC FORM.

Even in the absence of marked intestinal symptoms there may occur severe gastralgic paroxysms with profuse vomiting,and often with haematemesis.In other cases there may be a syncopal attack in which the patient presents symptoms of grave collapse,the severe cardiac disturbance requiring prompt measures for its relief.

CHOLERIFORM FORM.

The patient may present a picture resembling strongly that of Asiatic cholera in certain cases in which the chief localisation of the parasite is in the stomach and intestines.These cases have been particularly studied by Marchiafava (Centralbl.f.Allg.Path.u. Anat.,1894,v,No.10,418).The paroxysm usually begins with profuse vomiting and diarrhoea:the discharges may resemble those of cholera.The skin is cold,moist,and clammy.There is cyanosis of the lips and extremities; the pulse is rapid and thread-like.There may be cramps in the extremities.The condition closely resembles the algid stage of Asiatic cholera.If the paroxysm be not fatal,profuse sweating may follow,with an intermission in the symptoms.Post-mortem,the mucous membrane may, in the stomach and intestines,be found filled with malarial parasites;and actual thrombosis of the vessels of the mucous membrane,with superficial necrosis and

ulceration,may be produced by the latter.

PNEUMONIC OR DYSPNOEIC FORM.

A type of paroxysm,the symptoms of which are strongly suggestive of a pneumonia,has been described by Bacelli (Studien über Malaria,Berlin,1895) and others. Bacelli,however,as long ago as 1866,recognised this condition to be distinct from a true complicating pneumonia.It is certainly not an inflammation of the lungs;it is more probably an active congestion of the pulmonary vessels,and due to the capillaries of the lungs being the seat of a special localisation of the parasite of the disease.There is intense thoracic pain,great dyspnoea,and a painful cough.There may be moderate dulness over the affected lung with coarse,sonorous,and sibilant râles,as well as finer moist ones.Laveran has seen a fairly abundant haemoptysis following an acute dyspnoeic paroxysm.In other instances,despite the extreme dyspnoea,physical examination may be quite negative. The sputum is mixed with dark fluid and clotted blood.

HAEMOGLOBINURIC FORM.

Many authors assign to this type of the disease a special chapter under the heading of "malarial haematuria";for the affection is of great interest and clinical importance.In the graver fevers of certain malarious districts haemoglobinuria is not an uncommon symptom;but in temperate climates it is very seldom seen.The ultimate cause of its production is still in dispute.A continual destruction of the red blood-corpuscles is going on throughout every malarial infection. This occurs in various ways:(1)The parasites,developing within the corpuscles,form the black pigment,melanin,at the expense of the corpuscles in which they grow,the corpuscles becoming gradually decolourised and destroyed. (2)In many instances the red blood-corpuscles containing the parasite undergo a premature necrosis,becoming brassy-coloured and shrunken.(3)Sometimes the decolourisation of the corpuscles containing the parasite occurs quite suddenly,the corpuscles bursting,as it were,and setting free their haemoglobin in the blood stream.Thus, during an ordinary malarial attack there is always a certain amount of haemoglobin set free in the serum;but, as this amount does not pass beyond the limit of the quantity which can be disposed of by the liver,it does not appear in the urine.It is doubtless,in part,to this constant destruction of the red corpuscles,with the liberation of their haemoglobin,that the polycholia and slight jaundice,so commonly observed in malaria,are due. Ponfick estimates that up to one-sixth the total number of the red blood-corpuscles may be destroyed and disposed of in the economy without the haemoglobin appearing, as such,in the urine.If this destruction of the red blood corpuscles becomes unusually great,and the quantity of haemoglobin separated from the discoplasma of the red blood-corpuscles exceeds the amount which can be taken care of by the liver,haemoglobinuria will result.It is not,however,only the infected corpuscles which lose their haemoglobin in these instances:great numbers of their uninfected neighbours are equally affected,just as in the ordinary paroxysmal haemoglobinuria.Some substance,exclusively toxic to the discoplasma of the red blood-corpuscles must be present in

the circulation,or some change has taken place in the blood-serum by which it has lost its isotonicity;but what these changes are,and to what they are due,are by no means clear.There is much which might lead us to believe with Bacelli that some toxic substance,produced perhaps by the parasite itself,may be respobsible for these phenomena.In the present state of our knowledge it is difficult to understand why,however,haemoglobinuria should be so common in certain regions - West Africa and Greece,for example -and so infrequent in many other malarious localities.

Cases of this type must be regarded as among the severest manifestations of malarial fever.The same condition is known in West Africa as "black water fever". By many observers,particularly by the French,the term "bilious haemoglobinuric fever" has been used.Not infrequently the term "haematuric" is used,and,indeed, as the interesting researches of Joseph Jones show, actual haematuria often occurs.The haemaglobinuric attack is rarely the initial symptom of the infection. Usually the patient has had repeated attacks of malaria, the haemoglobinuria appearing suddenly with the relapse, or,if it be the first infection,the haemoglobinuric attack is preceded by several intermittent paroxysms.In cases where either in a relapse or in a primary infection the haemoglobinuria appears with the first actual paroxysm,there are often prodromal symptoms lasting for from several hours to sometimes several days.It is probable that these are associated with moderate fever,and often represent abortive paroxysms.There are loss of appetite,headache,indefinite pains in the extremities and back.It should be remembered that in many paroxysms of the more ordinary types of aestivo-autumnal fever the gradual onset of the paroxysm without chill is frequent:this is not true in the case of the haemoglobinuric paroxysm,which begins almost invariably with a severe shaking chill.This is followed by intense pain in the back,head,and extremities,and by profuse vomiting;the vomitus consists of a deeply bile-stained fluid.The face is flushed;the conjunctivae are injected;the pulse is rapid;and the patient is usually in a condition of grave anxiety and apprehension.Profuse diarrhoea is generally present;and the skin is usually markedly icteric in hue.

A somewhat reddish colour of the urine is noticed in connection with the early stage of the paroxysm.This hue,however,rapidly becomes deeper,and is finally an intense brownish-black colour with something of a greenish tinge,and a greenish-yellow on shaking.The vomitus becomes of a deeper colour - at first yellow, then green,and finally sometimes almost black.The fever is often high,the temperature reaching 106° F.,or even higher,in certain cases.There may be diarrhoea,the dejecta being green or brown in colour,while in other instances there is constipation.During the stage of fever the patient generally becomes jaundiced.There is usually little delirium,the patient being quite conscious and in a condition of great anxiety and agitation. He often complains of severe epigastric pain,which is possibly associated with repeated vomiting;in other instances the pains in the loins may be extremely severe,bearing,possibly,some relation to the intense renal congestion.

At the acme of the disease the urine is of a deep brownish-black colour,and deposits on standing an

abundance of a reddish-brown sediment.The amount varies considerably in different cases,in some being extremely scanty,in others amounting to as much as one thousand or fifteen hundred cubic centimetres.The specific gravity varies inversely to the amount of urine passed.As the amount is generally somewhat reduced,the specific gravity averages above normal.The reaction varies:it is generally feebly acid.There is usually an abundance of albumin.In some instances a test for the biliary colouring matters may be obtained.Kelsch and Kiéner assert that this is the rule at the height of the process,while Plehn (Deut.med.Woch.,1895,Nos.25,26,27),in eight cases was unable to obtain this test.The sediment consists of mucus,vesical epithelium,numerous granules and masses of pigment,renal epithelial cells,and,almost invariably, hyaline and granular casts with epithelial cells adherent thereto.In many instances blood-corpuscles may also be found,actual haemorrhages taking place into the kidneys.Often,however,the condition is a haemoglobinuria pure and simple,not a sign of a red corpuscle,- besides the profuse sediment of a brownish granular material, occasional epithelial cells,and casts,- being discoverable on the closest investigation.

Excepting for a slight trace of albumin with occasional casts, the urine,in the simplest and mildest attacks, clears up,and at the same time the temperature remains elevated nine or ten hours,and then falls quite suddenly to normal.In some instances a paroxysm of this nature is the last manifestation of the process,complete recovery following.In other instances there may be repeated intermittent haemoglibinuric paroxysms,ending perhaps in recovery.Very frequently,however,the condition is more severe.The fever lasts much longer;the vomiting and diarrhoea continue;the jaundice becomes more intense; there are perhaps occasional slight intermissions,but in the main the attack is continuous.The urine,as well as the fever,may show occasional temporary chages for the better,but these are of short duration,fresh esacerbations rapidly following.In some cases recovery may occur when the patient is apparently on the point of death; but more often,however,the urine becomes scanty and more albuminous,the patient becomes emaciated and pale, the eyes are sunken,the tongue is dru,the pulse is rapid and feeble,and eventually a fatal result follows.

One sometimes comes across cases that run an extremely rapid fatal course.The intial chill,fever,vomiting, and diarrhoea are associated with almost complete suppression of urine;that which is passed,often but a few drops,is intensely bloody.There is great agitation, intense prostration,the patient falling into a condition of profound collapse and dying within several days. Nephritis almost invariably follows the haemoglobinuric attack.In the milder cases it is transient and slight. In many more severe cases,however,the end of the paroxysm is followed by the symptoms of a well-marked nephritis,lasting sometimes for weeks and possibly even for months.In a certain number of instances this condition pursues a rapidly fatal course.The albuminuria and casts persist;the quantity of urine remains steadily below normal;the patient becomes uraemic;and the patient dies in the midst of delirium or coma or convulsions.

There are some malarious regions in which there is no malarial haemoglobinuria.In some regions where pernicious fevers are relatively common,haemoglobinuria is rarely seen.The cause for this is not very clear.In Rome,for instance,the disease is seldom seen.In certain parts of Africa,on the other hand,it is seen in its most fatal forms,and in Greece it is unusually common. It is not very frequent in most of the malarious districts of the United States of America.

The condition of the blood has already been referred to:it generally shows the aestivo-autumnal parasite. Predisposing causes appear to be any over-exertion or exposure,indeed,anything which reduces the vitality of the individual.Extremely interesting is the widespread idea in certain regions that quinine,which has so specific an action upon the parasites,may yet have an unfavourable influence,indeed,be the determining cause of the haemoglobinuric paroxysm.In Joseph Jones's very interesting memoirs (Med.and Surg.Memoirs,Vol.ii,1887), a number of assertions of this nature appear.More recently,Plehn - in an instructive article upon the black water fever of Cameroon - records his belief that in that climate,at least,the development of haemoglobinuria is often brought about by the administration of quinine; while the records of his cases of haemoglobinuric fever, treated with or without the specific malarial remedy, show that the more favourable course was pursued by those cases which were treated expectantly.This view, however,is not held by the majority of observers.In many of these cases the tendency toward spontaneous recovery suggests,certainly,that the the life of the parasite may be injuriously affected by the presence of the haemoglobinuria.

SCARLATINIFORM FORM.

The appearance during a malarial attack of certain cutaneous eruptions,as herpes,and especially urticaria, is very apt to be observed;but these are of no significance,and rapidly subside.The same,however,cannot be said of the diffuse scarlatiniform rash in cases of grave malaria.This form of pernicious fever was observed by the earlier physicians.Morton noted grave fevers with an eruption like that of scarlatina.Others have described cases of malarial infection in which a rash of that nature covered the whole body,and presented also erythema of the fauces,the erythema returning after desquamation in large scales had already lasted for three days.During the eruption the examination of the blood shows the presence of numerous aestivo-autumnal parasites.A typhoid condition followed the second eruption,accompanied by grave icterus and diarrhoea,the patient becoming progressively more anaemic.The parasites in the blood gradually diminish in number.The autopsy in these cases revealed the presence of areas of necrosis in the liver,with resulting emboli of hepatic cells in the suprahepatic veins,in addition to the lesions of malaria.This relapsing scarlatiniform erythema in malarial infection recalls those rare cases of the same eruption which have been described as occurring after certain infections - e.g., typhoid fever and pneumonia, and especially acute articular rheumatism.

CONDITION OF THE BLOOD IN AESTIVO-AUTUMNAL FEVERS.

This has been already considered in a previous section, when we saw that only the earlier forms of the parasite in its cycle of development are generally found in the peripheral circulation. These are the ring-like or amoeboid hyaline bodies, which are often quite free from pigment. As the later stages in the development of the organism are rarely found in the peripheral circulation, it is natural that the period shortly before and during the early part of the paroxysm should be that in which the smallest number of parasites is to be found on clinical examination of the blood; and this is actually the case. There are cases of aestivo-autumnal fever where, at this period, a prolonged search must be made before parasites are to be found. They are always present, however, after the lapse of a few hours. Indeed, after a careful investigation it is probable that there are no dangerous forms of malaria in which the parasite will not be discoverable. One usually observes the crescentic and ovoid pigmented forms of the organism after the disease has lasted for a week or two. Phagocytosis is very commonly to be noted and the pigment-bearing leucocytes are to be found throughout almost all the periods of the fever. The periodicity in the phagocytic action is much less marked than in the ordinary intermittent fevers. This is due in part to the presence at all times of the parasites in different stages of development, and in part to the early necrosis of the red blood-corpuscles which is so common in these fevers, the dead fragments being speedily engulfed and carried away by the colourless elements. Occasionally true macrophages, such as are seen in the spleen, may be found in the peripheral circulation: these may be enormous, ten times the size of an ordinary leucocyte. They sometimes contain coarse granules, much larger than any ordinarily seen in the blood, having somewhat the appearance of eosinophile granules. Entire smaller phagocytes with their included pigment or parasites or corpuscles, red corpuscles, - usually shrunken and brassy-coloured, including a parasite, and the parasite may be contained in these cells.

MALARIAL FEVERS WITH LONG INTERMISSIONS.

Besides the ordinary quotidian, tertian, and quartan intermittent fevers, there have been described, from the earliest times, other fevers with intermissions considerably longer: thus, fevers with intervals of five, six, seven, eight, nine, ten, eleven, and twelve days, or even longer, have been believed to exist. The observation of fevers with longer intervals, admittedly rare, was made bt Celsus, whi distinguished quotidian, tertian, and quartan fevers. It is but natural that, - consequent upon Golgi's first researches concerning the life history of the quartan and tertian parasites, and after the fact that a third parasite existed, whose cycle, under some circumstances, lasted but twenty-four hours, the fever in every instance being definitely concerned with the segmentation of a group of parasites, - many observers have suspected the existence of other varieties of parasites which in turn may be related to these rare fevers with longer intervals. In 1889, Golgi (Ziegler's Beitr., 1890, vii, 647) advanced the hypothesis that the crescent bodies, which we know to be connected with

the aestivo-autumnal parasite,might bear a definite relation to these forms of fever.He believed that they represented a form of parasite which underwent a long and slow development,lasting from seven to twelve days; that,finally,segmentation of the crescent forms occurred and paroxysms followed,just as in the case of the regularly intermittent fevers.This variety of parasite, however,differed in the length of time and the irregularity of the cycle of development,while the paroxysms, in like manner,recurred at irregular intervals,from seven to twelve days apart,or even more.Antolisei and Angelini 'Riforma Med.,1890,320,326,332) believed that fevers with long intervals were associated with this variety of parasite.Canalis (Fortschr.d.Med.,1890,Nos. 8 and 9) held that the aestivo-autumnal parasite also possessed two separate cycles - a shorter,lasting from one to two days,and a longer,associated with the crescent and ovoid bodies,lasting an indefinite length of time,three or four days at least.It is very seldom, however,that one observes clinically cases showing a regular recurrence of paroxysms at intervals longer than every fourth day.On the other hand,it is not so very unusual to meet with cases where a number of paroxysms have recurred at intervals of,appromimately,six to fourteen days.In all these instances one is generally compelled to depend largely upon the statements of the patient.An analysis of those cases which have been observed since the recognition of the parasite and its different varieties shows that these fevers with long intervals may be associated with any of the varieties of parasite which we know.Golgi noted the existence of such paroxysms in patients whose blood showed the aestivo-autumnal parasite.Bignami (Riforma Med.,1891,No. 165,p.169) and Pes (ibid.,1893,Vol.ii,p.759) described such cases occurring in connection with the tertian parasite;while the fact that they may be associated with the presence of any of the varieties of parasites which we know,alone or in combination,has been demonstrated by Vincemzi (Bull.R.Acc.Med.di Roma,1891-92,p.631; Arch.per le Sc.Med.,Vol.xix,F.3,p.263).Bignami appears to have been the first to narrate how these fevers may arise.As stated in the description of the parasite,the mere presence of the organism in the circulating blood is not sufficient to produce subjective symptoms.These appear first only when,from steady multiplication,the number of parasites contained in the circulation has reached a certain necessary quantity.With every period of segmentation their number appreciably increases.Not every fresh segment,however,continues to develop.Were this the case,every infection would become pernicious within a short period.With each paroxysm a very considerable number of young parasites is destroyed - so great a number,in fact,that many,indeed the majority,of cases of tertian and quartan fever tend towards spontaneous recovery,though,to be sure,relapses often occur.To what this destruction is due is as yet a matter of doubt.In how far it may depend upon the protective power of the blood-serum,or upon an active defensive phagocytosis on the part of the leucocytes,or,possibly, upon the deleterious effects of some toxic substance produced,perhaps,by the parasite itself at the time of

segmentation, is as yet largely a matter of speculation. It is, however, not an infrequent occurrence to see, more particularly in tertian or quartan infections, a severe paroxysm followed by a complete disappearance of the symptoms, while the blood shows a disappearance of the group of parasites. In such instances, through some means or other, the greater part, or an entire group of parasites, is destroyed at the time of segmentation. In these cases the result is usually complete apyrexia for a certain length of timemfrom several days to two weeks or even more, and then, after, perhaps, a little warning, a repetition of the paroxysms. In certain cases the first paroxysm may be followed by a period of apyrexia, ladting eight days perhaps before the development of a second febrile attack, and that, in turn, by another intermission of approximately the same length of time, and so on, the chart thus showing an intermittent fever with intervals of, perhaps, eight, or ten, or twelve days. Nevertheless, the characteristic parasites of tertian or of quartan fever are revealed by an examination of the blood. From all this it is evident, then, that the explanation of these fevers with long intervals is not to be found in a parasite whose cycle of development lasts an uncommonly great length of time, but in the fact that the first sharp paroxysm is followed by the destruction of so great a number of the parasites that a long period, - sometimes practically that of the period of incubation of the disease, - must be passsed through before the group again reaches a size sufficient to produce symptoms. The recurrent attacks represent recrudescences from attacks from which recovery has not taken place. Single paroxysms with long intervals, or, more commonly, one or two paroxysms occurring together with long intervals between them, may exist for a very considerable length of time in tertian or quartan infections. The imperfect method of treating malarial fever may in another class of cases be responsible for the occurrence of the paroxysms with long intervals. Many patients living in a malarious district are in the habit of taking large single doses of quinine immediately following any outbreak of fever. For example, a patient may have had paroxysms at intervals of ten days, and the third and fourth one showed the characteristic parasites in the blood. In this instance the patient, by taking a single dose of quinine after each paroxysm, accomplishes the same end which nature accomplishes in the other class of cases, namely the destruction of the greater part of the group of parasites, a relapse occurring about ten days after the previous attack. The same explanation is probably true in the cases occurring in aestivo-autumnal infections. There is no evidence to show that there is any such thing as a regular type of fever occurring at intervals longer than every fourth day. According to the variety of infection, the paroxysms in these cases differ in no way from those in aestivo-autumnal, tertain, or quartan fevers.

MIXED INFECTIONS.

Though somewhat uncommon, combined infections with one or more varieties of the malarial parasite may occur. Clinically, these cases present usually the features of an ordinary tertian, quartan, or aestivo-autumnal infection; and without examination of the blood, the presence

of the two parasites would often remain unsuspected. This is due to the fact that the two different varieties of the organism are rarely present each in sufficient number to produce symptoms at the same time.One type of the parasite almost always predominates,and is responsible for the clinical symptoms.Certain cases have been noted where a distinct alternation of symptoms has occurred;a period of quartan fever,for instance,being followed by a spontaneous recovery,and succeeded by a period of tertian fever,which,if untreated,pursues the same course,and gives way finally to a relapse of the quartan infection;the parasites of both varieties are present at the same time.The common combination is in temperate climates,at least,that of tertian and aestivo-autumnal fever.In rare instances complicated fever curves may arise from a combined infection,but this is very uncommon.

CHRONIC MALARIA.

In chronic cases of malarial infection the disease continues in the organism for months or even years.The condition is manifested by febrile attacks which are repeated at greater or lesser intervals,by enlargement of the spleen and liver,and by a secondary anaemic condition and its results.In malarial dostricts chronic infection is readily recognised by a special earthy complexion,an enlarged abdomen,and a torpidity and depression of spirits.Sometimes,however,in genuine chronic infections,especially if the fever is mild and if the attacks are repeated at long intervals only,the patients may be in good condition,with the exception of slight and transitory anaemia after the attacks,and may attend to their occupations with their usual activity.

CONDITION OF THE URINE IN MALARIAL FEVER.

There are no special diagnostic features to be observed in the urine in cases of malaria.There are no constant changes in the amount or in the specific gravity of the twenty-four hours' urine.The colour of the urine is somewhat increased,dur probably to the increased quantity of urobilin which is derived from the haemoglobin of the red blood-corpuscles destroyed by the parasites.The amount of urea excreted during the paroxysms is increased,just as it is during any other other acute febrile condition.Albumin is usually present in serious cases,sometimes in about 50 per cent.In many of these instances casts of the renal tubules may be found.Actual nephritis may occur,and it may be diffuse or haemorrhagic in character.Ehrlich's diazo reaction may be present in some of the cases.Concerning the increased toxicity of the urine during malarial fever, some valuable and interesting researches have been made by various observers.Brousse (Cited by Laveran,loc.cit.), studying the effects following the injection of the urine of cases of amlarial fever into animals,arrived at the following conclusions:"(1)The urotoxic coefficient calculated by Bourchard's formula,the mean coefficient being 0.464,rises during the paroxysm,and the physiological effects observed are those which usually follow the injection of urine - dyspnoea,myosis,falling of temperature,exophthalmos,and furthermore convulsions; (2)this toxicity is diminished during the period of convalescence in intermittent fever,very much below that

of the urine during the paroxysm,and moreover below that of the normal urine."Investigating the condition of the urine in three cases of malarial fever,- one a case of tertian fever and two cases of pernicious comatose malaria,- Roque and Lemoine (Rev.de Méd.,1890,p.926) conclude as follows:"(1)The pathogenic agents of paludism form,in the blood,a large quantity of toxic products, a great part of which is eliminated by the urine.This elimination os at its maximum immediately after the paroxysm,and lasts,generally,twenty-four hours,at least in the paroxysms of tertian fever."(2)Sulphate of quinine acts by favouring the increase of this elimination.(3) Certain pernicious fevers,showing a complete absence of toxicity in the urine,depend probably upon alterations in the kidneys and liver,and the return of the urinary toxicity should be considered a good prognostic sign. (4)Finally,it may be noted that in two cases recovery has followed a more increased elimination of toxines than that observed after the preceding paroxysms."In discussing this paper,Lépine justly remarks that injections should be made not only with the pure urine,but also with a solution of the salts of the urine made after calcination;by which means alone a reliable idea of the toxicity of the urine dependent upon organic compounds can be obtained.While finding the same general results as Roque and Lemoine,Botazzi and Pensuti (Lo Sperimentale,Firenze,1894,xlviii,232,254)dispute their conclusions after an elaborate control research,in ten cases.They collected urine during and after the febrile periods,and found that during the paroxysm the urine showed a less intense colour than afterward.During the febrile periods examination of the urine,with the ordinary reagents which are used in qualitative analysis, showed always a diminished amount of alkaline and earthy phosphates,while that voided after the paroxysm showed sometimes a considerable quantity.The specific gravity of the urine passed after the paroxysm was higher than during the paroxysm.They state that under other conditions the urotoxic coefficient has been shown to run parallel in the elimination of the potassium salts,while the presence of peptones in the urine increases appreciably its toxicity.Both these substances they found present in increased quantities in the urine passed after the paroxysm.The urobilin,as already stated,is present in increased quantities in the urine of malarial fever,and especially so in that following the paroxysm. The toxicity of this substance has been demonstrated by these authors,who found that the urine passed after the paroxysm,when decolourised,lost half its toxicity.They assert,in opposition to Roque and Lemoine,that there is no need to suppose the presence of special toxic substances of the nature of leucomaïnes to account for the toxicity of malarial urine after the paroxysm;the postassium,the phosphoric acid,the peptones,the urinary pigments,and especially urobilin,which are found in this urine in markedly increased quantities relatively to the normal urine and to that of the febrile period,are of themselves a sufficient explanation.The cause of the increased presence of these substances is not difficult to appreciate.The potassium salts and the pigments, which they believe to be the chief cause of the hypertoxicity,result from the destruction of the red blood-corpuscles,and the phosphoric acid and peptones are

doubtless due to disintegration and combustion of the albumins and nucleins of the cellular elements of the tissues. They affirm that they have been unable to discover any signs of a marked retention of toxic substances, held by Roque and Lemoine to be due to disease of the kidneys. They go on to state that: "We think that we have demonstrated (1) that in the malarial fevers the febrile urine is less toxic than that emitted during the apyretic stage; (2) that the urine emitted during the period of apyrexia is more toxic than normal urine; (3) that the toxicity of the urine of malarial patients augments constantly with the succession of febrile attacks, though in some cases this augmentation appears in the form of unexpected and irregular exacerbations; (4) that, as there is nothing specific in the course of the intoxications produced in rabbits with malarial urine, there is no need to suppose the presence of special toxins or substances of the nature of leucomaïnes, for the salts of potassium, phosphoric acid, the urinary pigments, the peptones, all of which substances are eliminated in increased quantities, are a sufficient explanation; (5) that the injection of febrile urine is followed by a slower intoxication, characterised by sopor, by increased diuresis, by diarrhoea, and mydriasis, while the apyretic urine produces a more acute effect, sometimes fulminating, characterised by clonic and tonic spasms and mysosis, 'exhorbitisme' spastic expiration; (6) that to explain this different picture one may suppose that with febrile urine the polyuria and diarrhoea are due chiefly to the increased richness in the urea, while the peptones may contribute to the production of sopor. In the afebrile urines the salts of potassium, the phosphoric acid, the urinary pigments, and especially the urobilin, manifest themselves as substances essentially convulsive, determine hypertoxicity. (7) Finally, besides the haemocytolysis and the destruction of the cellular elements of the tissues, and the firmation and elimination of toxic substances, there must exist intermediate factors which account for the absence of increased toxicity after the first febrile paroxysms and the irregular elevation and diminution in the urotoxic coefficient in some other cases." We may conclude, then, that while a distinct increase in the toxicity of the urine has been shown to be present after malarial paroxysms, its dependence upon specific products of the action of the malarial organism has not as yet been definitely established.

CONDITION OF THE BLOOD IN MALARIA.

This has already been very fully considered in a former part of this essay, and need not, therefore, be further discussed.

SEQUELAE AND COMPLICATIONS.

Regarding the appreciation of the nature of the sequelae and complications, there is probably no point in the history of the development of our knowledge of malarial fevers where so much confusion and misapprehension has existed as in this particular. The relation of the chronic cachexia and grave anaemia to malaria has long been recognised, as well as the existence of an acute post-malarial nephritis. The grave cerebral, nervous, and gastro-intestinal symptoms which may occur with acute malaria have been already referred to. Many observers, however, do even today, ascribe to the malarial poison the capacity of producing of itself a considerable number of other complicating processes ordinarily dependent on other specific causes. These observers have in particular described a "malarial pneumonia", "malarial dysentery", etc. When we consider the many ways in which simple malaria may be complicated or masked, the fact that such misapprehension should have arisen is not remarkable. In this direction the main possibilities are well expressed by Ascoli (Bull. della Soc. Lanc. d. Osp. di Roma, An. xii, 1891-92, 103) as follows: "Finally, in conclusion, we may distinguish the following clinical forms: (1) Malaria which simulates another pathological process. (2) A disease, the (ordinary) course of which is known, which, in an individual suffering with chronic malaria, progresses and develops anomalies in its course according to the stage of the cachexia. (3) A fresh malaria develops in a subject who is at the time in an apyretic stage of the disease or suffering from the remains of a former infection (combinata). (4) Different varieties of the haematozoa exist in the blood of a patient suffering from malaria alone (mista). (5) Two febrile diseases exist together and contemporaneously (concomitanti): (a) exerting a reciprocal influence detrimental to the organism (proporzionate); in certain of these cases the reciprocal influence is not manifest throughout the entire course; (b) each preserving its more constant and common symptomatology (associata). (6) The malaria may prepare the ground for the development of another acute infection, or it may follow after another infection has run itself out (consecutiva)". For the purpose of description, we may divide the sequelae and complications of malarial fever into, first, those sequelae or complications due directly to changes produced by the malarial parasites or their toxic products, and, second, true complications, mixed infections.

Regarding the sequelae and complications due directly to changes produced by the malarial parasites or their toxic products, in the section upon the pernicious fevers the acute symptoms produced by the special localisation of the parasites in the brain, lungs, or gastro-intestinal tract have already been discussed. To enter into the consideration of the acute choreiform and comatose cases, which might so readily suggest a mixed infection, is therefore quite unnecessary.

RELAPSES.

In malarial fever relapses are of very common occurrence. Indeed, most cases, unless treatment be thoroughly carried out, show recrudescences in the course of one or two or three weeks. These are clearly proven to be due to the fact that all the parasites have not been destroyed by the treatment. The few which escape form a nucleus for the development of new groups, which in the course of a weeks or two arrive at a degree of development sufficient to result in a fresh outbreak of the symptoms. The recrudescences are, ordinarily, in every way similar to the original attacks. There is, however, another variety of relapse which has been recognised for many years, namely, the reappearance of an infection many weeks or months after all symptoms have disappeared. Undoubtedly, many such cases are fresh infections. There are, however, cases where a fresh infection can be definitely ruled out, while the malarial nature of the process is undoubted. There can be little doubt as to the nature of the case, though the absolute proof, the discovery of the parasite, may be wanting. The explanation of these cases is difficult. It is highly improbable that the parasite has remained present in the blood, passing through its ordinary cycle of development, and yet some form of the parasite must exist throughout this time. Bignami suggests some form of the organism may persist in some of the internal organs, possibly within the protoplasm of some of the cellular elements, which perhaps we have not been able to discover - e.g., a non-staining spore.

MALARIAL CACHEXIA.

The dyscrasia known as chronic malarial cachexia is the commonest sequel of malarial fever. It is well known that in malarious districts many patients allow an infection to continue for weeks, months, or perhaps years, without ever attempting a systematic or thorough treatment. Naturally, the result is a serious drain upon the vital resources of the individual. The course of such a case is commonly as follows: The patient has several paroxysms, and takes a few grains of quinine, which are followed by a disappearance of the fever; or, after a week or so of paroxysms which have been untreated, the fever disappears spontaneously. Frequent relapses occur, which are improperly treated or allowed to take their own course. In some instances of aestivo-autumnal fever a patient may remain for a long time with a slight and irregular fever, no sharp, definite, malarial paroxysms being observed. The first result of a continued process of this nature is the gradual development of an anaemia which usually becomes marked, and is sometimes extremely grave. The patient has a sallow, grayish-yellow colour; the lips and mucous membranes are blanced; the tongue is often coated; and there is frequently oedema of the dependent parts. Sudden motion or exertion is followed by vertigo or fainting. The gait is tottering and unsteady; and marked general tremor may be observed. The spleen is usually greatly enlarged, sometimes reaching to the right of the median line. Indeed, some of the largest splenic tumours which occur may be seen in these cases. The hepatic flatness is increased in extent; the

border is often palpable, reaching sometimes a considerable distance below the costal margin. Except for the anaemia, the examination of the blood during an afebrile stage may be quite negative. More commonly occasional parasites or pigmented leucocytes may be found, while in aestivo-autumnal infections the characteristic crescentic or ovoid pigmented bodies are usually to be seen. Chronic cachexia may follow any variety of infection. In the majority of instances, however, it represents an untreated aestivo-autumnal infection, and in these instances the crescentic and ovoid forms of the parasite may be found. The same condition also frequently follows repeated attacks, even though the individual attack has been actively treated. The tendency towards dropsical transudations is generally decided, and at times may give rise to confusion. Thus, in several instances there have been observed cases of moderate anaemia with quite marked oedema of the dependent parts, and complete absence of fever, where, owing to an unsatisfactory history and the failure to find parasites in the blood, the true nature of the process was wholly unsuspected until the appearance, within several weeks, of a relapse. Gastro-intestinal disturbances are very common in malarial cachexia; and the patient may be reduced to a distressing condition of marasmus, where he is an easy prey to all sorts of complicating infections, through the grave anaemia, with diarrhoea, oedema of the dependent parts, and the enormous splenic tumour - sometimes called "ague cake". Children not uncommonly suffer from chronic malarial cachexia; and in these patients, owing to the irregularity of the symptoms, the true nature of the process is often unsuspected. It may lead to the most intense grade of infantile atrophy. The child becomes greatly emaciated; the sallow, grayish-yellow, parchment-like skin hangs in folds; and the mucous membranes are blanched. The spleen is always enormously enlarged. There are occasionally slight febrile attacks, the child becoming cold and blue, or, perhpas, showing now and then a slight eclamptic attack. There are peristent gastro-intestinal disturbances, - e.g., vomiting and diarrhoea, - as well as, perhaps, diffuse bronchitis.

MALARIAL ANAEMIA.

It is a well-known fact, apparent both from clinical observation and examination of the blood, that, after every febrile disease of a certain gravity and duration, there is a diminution in the number of the red blood-corpuscles; but in no other infection is anaemia produced with the same rapidity and to the same extent as in malaria. This fact was within the knowledge of physicians for some time before the discovery of the malarial parasite. The anaemia may be of various forms. For example, four types of post-malarial anaemia are distinguished by Bignami and Dionisi as follows: (1) Anaemia in which the examination of the blood shows alterations similar to those observed in ordinary secondary anaemia, differing from these cases only in that the leucocytes are diminished in number. These cases often show well-marked oligocythaemia; oligochromaemia relatively greater; more or less poikilocytosis; nucleated red corpuscles or normoblasts. The leucocytes, as already stated, are diminished in number, while the relative

proportion of the large mononuclear forms is increased at the expense of the polymorphonuclear cells.A fatal course is pursuedd by a few of the cases,without any change in the haematological condition,though the greater number go on to recovery.(2)Anaemia in which the blood shows changes or alterations similar to those common in pernicious anaemia,that is,marked oligocythaemia;oligochromaemia relatively less;marked poikilocytosis;nucleated red corpuscles,for the most part gigantoblasts;leucocytes,diminished in number with an increase often in the small mononuclear forms,and a diminution in the polymorphonuclear varieties.Patients thus afflicted almost surely die.(3)Anaemia showing the ordinary characteristics of secondary anaemia,excepting for the complete absence of regenerative forms - nucleated red corpuscles.These cases are progressive and fatal;and,as already stated,no evidence of regenerative activity is to be found in the bone-marrow at the autopsy.(4)In prolonged cases of malarial cachexia chronic secondary anaemias occur;and they are remarkable for the small number of nucleated red corpuscles present and the marked reduction in the number of the leucocytes,particularly of the polymorphonuclear variety.A favourable sign,pointing to a rapid regeneration,is to be found,however,in those post-malarial anaemias which do not show after the clearing up of the infection a leucocytosis similar to that in ordinary secondary anaemia.

NEPHRITIS.

The intense acute nephritis,- which,as described in a previous section,may follow malarial haemoglobinuria,- most strikingly brings to one's notice the grave damage which the kidneys may suffer in certain acute malarial infections,either from the direct action of some toxin produced by the haematozoa or from the presence in the circulation of injurious substances,due indirectly to the action of the parasite.The kidney,however,rarely escapes a certain amount of damage in any severe malarial infection.The nephritis following malarial fever is usually a mild and acute diffuse process similar to that observed in any infectious disease.In some instances,as stated in the section on malarial haematuria,the course may be rapid and fatal;in the majority,however, the prognosis is favourable,and complete recovery occurs.In these instances of malarial nephritis there is nothing absolutely characteristic,clinically or pathologically,of the process;and in some cases it is possible that the malarial poison may be responsible for a fatal chronic diffuse nephritis.

AMYLOID DEGENERATION.

An occasional outcome of a malarial attack is amyloid degeneration.Two cases were reported by Frerichs, and the reports of several others appear in the literature of the disease.These cases have followed after a long series of febrile attacks,those which have been carefully studied having been aestivo-autumnal or obstinate quartan fever.The clinical symptoms are those of nephritis accompanied by an extremely rapid cachexia, ending fatally ,as a rule,within sveral months.The blood in these cases may show the condition first noted by Ehrlich as of grave portent,namely,complete absence

of nucleated red corpuscles and eosinophile cells, and reduction in the number of the leucocytes. At the autopsy the marrow of the long bones shows no evidence of an attempt at regeneration, but appears to be entirely fatty.

GASTRO-INTESTINAL DISEASE.

A case of extensive atrophy of the gastro-intestinal mucosa, apparently following an acute malaria, has been reported by Pensuti. Constant diarrhoea followed the attack, resulting in great exhaustion and death from broncho-pneumonia in three months. The case cannot, however, be considered as wholly convincing, though Bacelli was inclined to believe that the change was directly due to the action of some toxic substance connected with the malarial infection.

DISEASE OF THE LIVER.

We have already seen that the occurrence of a true atrophic cirrhosis of the liver, as a sequel to malarial fever, has been insisted upon by many observers. There are many instances which would lead us to believe that this may, in some instances, occur; but, clinically, in temperate climates at least, such cases are rarely met with. In few instances does one meet with a true atrophic cirrhosis of the liver in which other etiological factors of importance have not also been present. On the other hand, chronic hepatitis, resulting usually in an increase in the size of the liver, is commonly observed in malarial cachexia and following repeated malarial infections. There are evidently no distinct clinical symptoms that can be referred to the changes in the liver.

NERVOUS DISEASES.

In connection with malarial fever various cerebral paralyses have been described. They are usually transitory, disappearing under treatment, and are due probably to circulatiry disturbances induced mechanically by the parasites: they are almost always cortical in nature. The nervous symptoms are more commonly irritative than paralytic in acute malaria. Occasionally there occur symptoms suggestive of involvement of the spinal cord; and several Italian observers have reported cases where the phenomena strongly suggested disseminated sclerosis. In all these instances the parasites were found in the circulating blood, and recovery followed treatment by quinine. In one of Torti's cases (Bull. d. Soc. Lanc. d. Osp. d. Roma, 1891, xi, 217) there was, however, not fever, notwithstanding the presence of active parasites in the blood. In such instances it is easy to conceive that without examination of the blood a diagnosis would be quite impossible. Da Costa (internat. Clinics, 1891, iii, 246) has also reported a case of paraplegia with intention tremor, severe headaches, bitemporal hemianopsia, and mental symptoms, where the blood showed the aestivo-autumnal parasites. Recovery occurred under quinine. The cases of so-called acute ataxia reported by Kahler and Pick (Beitr. z. Path. u. Path. Anat. des Centralvervensystem, Leipzig, 1879) were probably truly malarial. Bastianelli and Bignami (Bull. d. R. Acc. Med. di Roma, 1893-94, Anno xx, p. 221) have reported a case showing symptoms of the so-called electric chorea or Dubini's disease. Lesions secondary to the cerebral localisation of the

parasites were considered by them responsible for the process.The latter was associated with a continued fever,the nature of which was not,at first,determined. Examination of the blood later showed it to be due to an aestivo-autumnal malarial infection;and recovery under the influence of quinine occurred in due course.Provided that treatment be begun in time,all of these processes coming on with acute malarial fever are esentially favourable in their course.The fever,however,according to Boinet and Salibert,may be followed by both spinal and cerebral permanent paralyses.Though definite proof of their malarial origin is wanting,cases of peripheral neuritis following malarial fever have been reported. From what we know,however,of the pathogenesis of the disease,we may readily believe that malarial fever may be followed by acute degenerative lesions in the peripheral nerves,in the same way as these occur in connection with other acute infectious diseases.Emboli of the melaniferous leucocytes in the capillaries have been alleged by Poncet to be productive of a retinitis and a retino-choroiditis.Though by no means proven, some good observers affirm that there was some predisposing relation between malarial fever and Raynaud's disease or symmetrical gangrene.Just as in the case of any acute infection,various mental affections have been seen to follow malarial fever;but there is nothing specially characteristic in these cases.

There now remain to be described the second class of cases,namely that of the true complications and mixed infections occurring in the disease under consideration:which latter,indeed,like any other acute process,is subject to various complications,many of which are a result of mixed infections with other pathogenic agents.As already mentioned,many of the symptoms caused by mixed infections were believed by the older observers to be due directly to the malarial poison.Since their time,however,with our increased facilities for study and appreciation of these conditions, the dependence of the complication,in the vast majority of instances,upon a true mixed infection has been established.

RESPIRATORY AFFECTIONS.

Well-marked pulmonary symptoms,- such as dyspnoea, pain,and haemoptysis,- occurring during the paroxysm have been described by many observers in connection with pernicious fevers.These symptoms,dependent probably upon the special localisation of the parasites in the pulmonary capillaries,are to be sharply distinguished from true pneumonia,which may,and not infrequently does,complicate a malarial attack.Again,in certain instances an ordinary acute pneumonia may present an intermittent fever which simulates quite closely the chart of intermittent malarial fever.These cases, however,may be readily reconnised by the absence of the parasite from the circulating blood.Such cases have been described by Wunderlich,Jaccoud,Bertrand, Andrew Clark,and others,while Ascoli (Bull.d.R.Acc.di Roma,xv,1888-89,355) gives an excellent chart.True acute pneumonia and malarial fever may,however,coexist. In these instances the course of the pneumonia may be but little influences by the coexisting malarial fever,

while in other instances the exacerbations and remissions of temperature may be quite marked. Here the pulmonary process is a genuine croupous pneumonia, due to infection with the diplococcus lanceolatus, as has been shown by Marchiafava and Guarnieri (Bull. d. R. Acc. Med. di Roma, 1888-89, xv, 355). Its course is quite uninfluenced by the administration of quinine, and its connection with malarial fever is purely accidental, unless, as it may be in some instances, a preceding malaria has prepared the ground for the pneumococcus infection by reducing the vital forces of the individual. Pneumonia occurring in individuals suffering with chronic malarial cachexia appears to pursue an unusually malignant course, owing, doubtless, to the reduced condition of the patient. Retarded resolution and organisation of the exudate are said by Ascoli to be not uncommon in these cases. Bronchopneumonia is also occasionally observed in association with malaria; but there is, however, no direct relation of the former to the latter, as the infection is purely of a secondary character. In acute pernicious malaria certain observers have described the occurrence of symptoms suggesting pleural involvement where, on autopsy, nothing was to be found. In other instances pleurisy and malarial fever may coexist, although there is nothing whatever to show that this pleurisy is not an entirely separate process from the malarial infection, and it is not influenced by the administration of quinine. There is nothing abnormal in the, besides this, in the clinical or pathological course of such a pleurisy; and these cases are not to be confounded with the pleural exudates which may occur in cachectics.

TYPHOID FEVER.

There has been much discussion regarding the relations between malarial fever and typhoid fever; and in certain countries these relations are probably more generally misunderstood than any one point in connection with the febrile diseases. Since the discovery of the malarial parasite, with our modern methods of diagnosis, there is no reason for the existence of any such confusion at the present day. The great similarity between the symptoms in certain cases of aestivo-autumnal fever with typhoid fever is well-known. There is, however, no excuse whatever for the physician who today fails to recognise the malarial nature of such a fever after a few days' observation; for, the parasite being always present, the question will be definitely settled by a simple examination of the blood. The term typho-malarial fever is one that is known to the profession everywhere. It was supposed that in malarious districts there existed a continued fever which depended upon the combined action of two poisons, that of malaria and that of typhoid fever - true "proportionata", in the sense of the old Italian observers. This fever was supposed to be markedly resistant to quinine, and to betray its malarial nature by the frequency with which rigors occurred. We know today, however, that typho-malarial fever as a distinct entity does not exist. Rigors occurring in the course of typhoid fever are by no means uncommon, but are of themselves wholly insufficient evidence on which to base a diagnosis of malaria. We know, on the other hand, that there exist in certain localities no malarial fevers which resist for more than three or four days

the action of quinine.True complications of typhoid fever and malaria may occur,but they are very rare. Typhoid fever may be acquired by a patient suffering from acute or chronic malaria.A fresh malarial infection may break out,or a slumbering infection may come to life again,during the course of typhoid fever.But this condition is uncommon,and in no way justifies the term typho-malarial fever.There is little doubt that the enormous majority of cases referred to today as typho-malarial fever are cases of typhoid fever,pure and simple.Too much stress cannot be laid on this point, for the groundless assumption that there exists a fever due to the combined action of the typhoid and the malarial poison,pursuing a fairly characteristic course and calling,from its malarial nature,for the continued use of quinine,has exercised in the past,and is perhaps exercising today,an extremely injurious influence upon present-day knowledge.The picture in the case of true mixed infection of typhoid and malarial fever may be most varied.If a fresh malarial attack or a relapse break out during the course of typhoid fever,well-marked indications of the paroxysms,varying according to the type of parasite present,may be observed,as shown admirably by the charts published by Gilman Thompson (Trans.Ass.Amer.Phys.,1894,110).In these instances the blood shows the presence of the parasites;these,with the symptoms dependent upon them,disappear immediately after ordinary doses of quinine.On the other hand,there may be almost an absence of the symptoms on the part of the malarial parasite,if the typhoid fever develop in the course of latent or chronic malarial infection.

INTESTINAL AFFECTIONS.

During acute paroxysms,particularly in children,the occurrence of diarrhoea is well known.The changes produced by the malarial parasite in the intestine in certain acute pernicious cases have already been considered; the acute choreiform pernicious paroxysm is truly malarial in nature.There is nothing,however,to show that the more chronic dysenteries and diarrhoeas,often associated with cachexia,are in any way directly connected with the action of the malarial poison,excepting in so far as this may have prepared the gorund.It is not impossible to conceive that severe infections might follow directly upon an acute choreiform attack.There are several cases on record where the Amoeba coli had been found in the dejecta of patients suffering simultaneously with acute malaria and dysentery.In all of these instances the intestinal process might well have been directly ascribed to the malarial poison.It is exceedingly probable that many of these post-malarial intestinal affections in tropical climates may be in reality due to a mixed infection with the two protozoa, considering the frequency with which the Amoeba coli is associated with tropical dysenteries.

TUBERCULOSIS.

The direct antagonism of tuberculosis to malarial fever and the converse has been affirmed by various observers,and particularly by Bondin (Treatise on the Intermittent Fevers,Paris,1842).This observer points out that tuberculosis was rare in countries where malaria existed,and that where tuberculosis was common malaria was rare.This assumption has exerted a certain

influence on the minds of many.Experience,however,has shown that it lacks foundation.In many of the districts where malaria is common it is true that tuberculosis is unusual,owing to certain climatic influences.In the northern regions,where tuberculosis is more common, malaria,as is well known,is,relatively,infrequent.In other regions we find malarial fever and tuberculosis side by side,intimately associated,occurring,by no means infrequently,in the same patient.Marchiafava (Bull.d. Soc.Lanc.d.Osp.d.Roma,1891,Anno xv,186),indeed,as well as others,from actual clinical experience are inclined to believe that chronic malaria is not an unimportant predisposing cause to pulmonary tuberculosis.Others, however,affirm the contrary.

MISCELLANIOUS INFECTIONS.

It is not so rare as is generally supposed to find infections with other pathogenic organisms;thus,one may observe furunculosis,parotitis,tonsillitis,and acute rheumatism,while,in one case studied by Barker,there was a general infection with the streptococcus pyogenes.Bacelli has observed cases of exanthematous diseases complicated during convalescence by characteristic malarial fever,while Antolisei and Laveran testify to the same effect in cases of smallpox.

SUNSTROKE.

It is probaly not very common to find chronic malarial fever complicated with thermic fever or sunstroke. Bastianelli and Bignami (Bull.d.R.Acc.Med.d.Roma,1893-94,Anno xx,p.151)have demonstrated in an interesting manner the frequency with which such cases have,in Italy,been considered as essentially malarial in nature. The pernicious malarial fevers are particularly common at the hottest season of the year,while the individuals most subjected to malarial infection are also often those who work bareheaded in the fields,exposed directly to the sun's rays.These observers called attention to the fact that a number of instances of what has been considered pernicious comatose malarial fever have been reported in which,at autopsy,only cerebral hyperaemia, pulmoary hypostasis,and slight degenerative changes in other organs were observed.In some of these cases no malarial parasites were to be found;in others,evidences of a recent infection;in others,perhpas the evidence of a recent infection with the presence of a small number of active parasites - far too few,however,to account under ordinary circumstances for such grave symptoms. Cases of this nature have led some observers to assume that a very small number of parasites might give rise to severe pernicious symptoms,owing to their excessive malignancy.It is much more probable,however,that the process represents a complication of malarial fever with insolation,which might occur in an individual with active malarial fever or in one who has recently recovered from an attack.Indeed,it is not impossible that a preceding malarial infection may render the individual more subject to such attacks by reducing his vitality and strength.

OBSTETRIC AND SURGICAL MALARIA.

The occurrence of post-partum and post-operative malarial fever has often been described;and it is too common at the present time to ascribe elevations of temperature during the first few days after operation

and during thr puerperium to malarial fever.Undoubtedly, the reduced condition of the patient during these periods might,and probably does,favour a recrudescence of the latent malarial infection.It is,on the other hand, probable that the majority of instances of supposed post-partum and post-operative malaria have no connection whatever with true malarial fever,but represent simply a septic infection.

D I A G N O S I S.

REGULARLY INTERMITTENT MALARIAL FEVERS.

It is usually a comparatively simple matter to recognise the regularly intermittent, tertian and quartan fevers. The regular paroxysms with their three stages of chill, fever, and sweating are so characteristic as to leave little doubt in most instances concerning the nature of the process. The anaemia and the enlarged spleen, which are present in the vast majority of instances, are also important from the point of view of differential diagnosis. Occasionally paroxysms are very closely similar to the malarial access may occur from other infectious causes, and sometimes the regularity with which the individual paroxysms may succeed one another may lead to errors in doagnosis. The paroxysms, however, in malaria differ in certain respects from those occurring in most other acute infections. Thus, the average duration of the malarial paroxysm, if we estimate the course from the time the temperature passes 99° F. until it again falls below this point, is from ten to twelve hours, while in other infections the course is often materially shorter. There may be, of course, mild malarial paroxysms which last but four or six hours, but in these the temperature is correspondingly moderate. One rarely observes in malarial fever temperatures of 104°, 105°, or 106° F. in a paroxysm lasting as short a time as six hours or even less. There are cases on record of septic infection in which, for a considerable time, chills closely simulating those of malarial fever occurred, while the anaemia and enlarged spleen were also present. The chief difference noted was the marked difference in the length of the paroxysms, which were sometimes as short as four or five hours, the temperature reaching, perhaps, within this time a point as high as 106° F. The same may be true of the chills which are not so infrequently seen during the course of typhoid fever - chills caused, doubtless, by auto-intixications as yet not understood. One is justified in the suspicion that the fever is not malarial in origin whenever the temperature rises as high as 104° F. and the paroxysm lasts no longer than six hours.

Paroxysms, most closely simulating those of malarial fever, may, however, at times occur from other infections. Thus, cases are on record in which there were observed typical quotidian paroxysms lasting from ten to twelve hours, and beginning nearly at the same hour on two successive days, which were considered to be malarial in nature, for which, however, otitis media acuta was ultimately discovered to be responsible. But the intermittent fever that is associated with pulmoary tuberculosis is most commonly confused with malaria. It is probably no exaggeration to say that the majority of cases of pulmonary tuberculosis arising in the malarial districts of most temperate climates are, at some time in their course, mistaken for malarial fever; and the same is probably true of tropical zones also. Intermittent fever, recurring often at fairly regular hours on succedding days, is the rule at some stages, earlier or later, of

pulmoary tuberculosis,while acute chills may occur.It is natural that the patient should ascribe such symptoms to malaria;there is,however,no excuse today for such error on the part of the physician;for the examination of the lungs,sputum,and blood will determine the diagnosis;and the sallow colour,the anaemia,and the enlarged spleen will serve to distinguish the malarial process from tuberculosis,where,though the face be pale,the lips and mucous membranes show usually a good colour, while the splenic enlargement is rare.

One may sometimes confuse with malaria the chills which often occur in the course of gonorrhoea or those following catheterisation or the passing of sounds into the urethra.The latter should always be examined, therefore,in doubtful cases.In some cases of grave septicaemia following gonorrhoea there may be little or no evidence of an actual urethritis.Here the examination of the blood will immediately settle the question.In the one instahce there is leucocytosis without malarial parasites;in the other,a normal or reduced number of leucocytes with the presence of the malarial parasite. A positive diagnosis in all these cases alone can be made by having recourse to an examination of the blood.

Examination of the Blodd.

An oil-immersion lens is absolutely necessary for the satisfactory examination of the blood;and it goes without saying that a relaible microscope is also essential.Though much valuable work has been done with dry lenses and lower powers,it is folly to attempt careful work without better means.The simplest and best method of studying the malarial parasite is the fresh blood at the bedside or in the consulting room.The steps towards the preparation of the specimen are quite simple, though certain precautions must be rigidly adhered to. The cover-glasses and the slides must be washed in alcohol carefully,in order to remove all fatty substances: they should always be washed immediately before use.The blood may be taken from any part of the patient's body, though the lobe of the ear is perhaps preferable,inasmuch as it is least sensitive and more readily approached than the finger-tip,while a smaller puncture will draw more blood.The method is also more satisfactory than the puncture of the finger,in that the patient cannot so readily observe the proceeding - a point of considerable importance in nervous patients and in children.The ear is first thoroughly cleaned;the lobe is then punctured with a small knife or lancet.For the most careful procedures it is advisable to wash the ear with soap and water,and afterwards with alcohol and ether. But,practically,it is often advisable to make as few preparations as possible,and unless the ear or finger be extremely dirty one may proceed at once.A pin or needle will,of course,answer the purpose,but it is as well to remember that a stab made with by a round blunt-pointed instrument is much more painful than that by a sharp-cutting edge,while a considerably deeper stab is required to draw a given quantity of blood.If a very sharp spear-pointed lancet be used,and the lobe of the ear taken firmly between the fingers so that the skin is held tense,very slight pressure with the tip of the lancet will cause an incision deep enough for all purposes.This process is almost without pain to the

patient.Even a sleeping infant may have blood taken from it without awakening by the cafeful use of this method.The freshly cleaned cover-glass,after the first several drops of blood have been wiped away,is taken in a pair of forceps and allowed to touch the tip of a minute drop of blood.It is then placed immediately upon a perfectly clean slide.It is well,if a third person be present,to allow the slide to be vigorously rubbed with a clean linen cloth just before the application of the cover-glass.The spreading out of a drop of blood will thus be considerably facilitated.If the slide and cover be perfectly clean,the blood will immediately spread out between them,and,unless the drop of blood be too large,the corpuscles may be seen lying side by side entirely unaltered in their main characteristics.The drop of blood which is taken should be very small unless the patient be very anaemic,and care should be taken that the tip of the drop only touch the cover.If the cover be placed rudely against the drop and pressed perhaps also against the ear,the blood may so far spread out that the process of drying may have begun at the edge of the drop before the glass is laid upon the slide.The specimens will remain in good condition for a considerable length of time,an hour or more - long enough to be thoroughly examined.If one desire to observe the specimen for a greater length of time,the periphery of the glass may be surrounded by paraffin or vaseline.In this manner we may see the parasites living and in active motion,while the most exquisite examples of phagocytosis may be observed.By enclosing the specimen in paraffin or vaseline the preparations may,if handled carefully,be carried from the residence of the patient to the consulting room;but for this purpose dried and stained preparations should be employed.

It is not a difficult thing to stain a specimen: there is an art which is soon acquired by practice. Stained specimens are of especial assistance in the detection of the unpigmented hyaline bodies,particularly the pale tertian forms and those of the aestivo-autumnal parasites.A small drop of blood flowing from the lobe of the ear or the finger-tip is collected upon a perfectly clean cover-glass,which is immediately placed upon another glass.The drop of blood,if the two covers be perfectly cleaned,spreads out immediately between the glasses.The cover-glasses are then drawn apart.If neither glass be lifted or tilted during this process,they will slide apart readily without sticking. If the glasses have remained together so long that they have begun to adhere,one may be sure that the specimen will be no longer perfect.The glasses,thus prepared, are allowed to dry in the air,which they do usually in the course of a few seconds,and may then be preserved for an almost indefinite length of time.To prepare them for staining,the glasses should be heated upon a copper bar or in a thermostat at a temperature of 100° to 120°C.for two hours,according to the method of Ehrlich,or they may be placed,according to the method of Nikiforov,for two hours in absolute alcohol and ether.Most of the basic aniline nuclear dyes stain the malarial parasite readily.The simplest method is perhaps to stain with a concentrated aqueous solution of methylene blue or Löffler's blue,which consists of 30 c.c. of a concrentrated alcoholic solution of methylene blue and 100 c.c.of a solution (1 : 10,000 of caustic

potash.The specimens in either instance should be stained for from thirty seconds to a minute,washed in water,dried between filter-papers,and mounted in oil or balsam.The nuclei of the leucocytes and parasites will be stained a clear blue,while the red corpuscles will be unstained.The following method should be employed in order to obtain a contrast stain:The cover-glass specimen,after fixing in absolute alcohol and ether from four to twenty-four hours,is placed for a few seconds - thirty seconds to five minutes - in a 0.5 per cent. solution of eosin in 60 per cent.alcohol,washed in water,dried between filter papers,and placed for from thirty seconds to two minutes in a concentrated aqueous solution of methylene blue,or in Löffler's methylene blue,washed in water,and dried between filter papers, and mounted in Canada balsam.A blue colour is given to the nuclei of the leucocytes and the parasites,while the red corpuscles and the eosinophile granules are stained by the eosin.A modification of Romanowsky's method gives very satisfactory results.Two solutions are necessary - a saturated aqueous solution of methylene blue and a 1 per cent.watery solution of eosin.The older the methylene blue solution the better the results.The staining mixture should be made just before it is to be used.To one part of the filtered methylene blue solution about two parts of the eosin solution are added.This is carefully stirred with a glass rod and poured into a watch-glass;it should not be filtered after the mixture has been made.The cover-glasses, fixed according to the methods above described,or hardened in alcohol for from ten or more minutes,are allowed to float upon the top of this fluid.The specimens are covered with another inverted glass,and the whole by an inverted cylinder which is moistened on the outside.Good specimens are obtained in from half an hour to three hours - best in two or three hours.The simple stain with methylene blue is perfectly satisfactory for rapid work in the consulting room,though sufficient experience,of course,to be able to distinguish precipitates which may be present in the staining solution from parasites must be possessed by the observer.Though the results are uncertain,the experienced observer may obtain sufficiently good specimens for diagnosis in many instances by rapid heating of the cover-glass over the flame for a few minutes.

A positive sign of the malarial nature of the disease is,of course,the finding of the malarial parasites in the red blood-corpuscles.In some instances where the parasites may be very scanty or absent,the presence or absence of a leucocytosis is an important diagnostic sign.As already mentioned,the leucocytes in malarial fever are normal or diminished in number,whereas in almost all processes with which the acute intermittent malarial fever may be confounded there is a well-marked leucocytosis.This is the case in all the septic infections which are most likely to be confounded with tertian and quartan fever;it is also true of tuberculosis,at least when accompanied by intermittent fever.The presence of a marked leucocytosis is strongly presumptive evidence against the existence of malarial fever.In some instances where very few parasites are present the finding of pigment-bearing leucocytes may be an important aid in diagnosis.The examination of the blood will determine the diagnosis,while well-marked remissions and

almost invariably, actual intermissions, usually occur. Between tertian and quartan infections the differential diagnosis may readily be made in the fresh specimen, less distinctly in the stained. The larger and more actively amoeboid, pale tertian parasite with fine brownish, actively dancing pigment granules may be readily distinguished from the smaller, less active, more refractive quartan parasite with its coarser, more slowly moving, and darker granules. In the case of the tertian parasite the red corpuscles may be seen to become expanded and pale with the growth of the organism, while in the quartan parasite the corpuscle is shrunken and of a deeper, more brassy colour. If the blood be examined just before or during the paroxysm, the more irregularly segmenting tertian organisms, with their numerous - twelve to thirty - segments, may be clearly distinguished from the smaller regular forms in quartan fever with their fewer - six to twelve - segments. In either instance one may usually readily determine the presence of one or more groups of parasites. As a rule, one may also easily make out combined infections with quartan and tertian parasites, which, though very rare, do exist in certain cases. One should be able to make a differential diagnosis in the stained specimen by observing the size of the pigment and the parasite, as well as the behaviour of the red corpuscle - pale in one instance, taking a deep eosin stain in the other - and the characteristics of the segmenting forms. The therapeutic test is usually sufficient if it be impossible to make a microscopical examination of the blood; thus, in the regularly intermittent fevers there is rarely any recurrence of the fever after forty-eight hours from the beginning of the administration of quinine. In this climate at least, there are no signs of the fever to be found after the lapse of twenty-four hours in the case of tertian infection.

AESTIVO-AUTUMNAL FEVERS.

The more irregular aestivo-autumnal malarial fevers are not nearly so easy to recognise as the regularly intermittent tertian and quartan fevers. In some instances, where the paroxysms are of shorter duration and occur at regular intervals, usually quotidian, the diagnosis may be as self-evident as in the regularly intermittent fevers. The longer paroxysms, occurring at intervals of approximately forty-eight hours one from another, with their less rapid rise, but with a complete intermission between them, are also generally easily recognised when we take into consideration the anaemia, the enlarged spleen, and the herpes labialis which are so commonly present. When, however, from any of the various causes above mentioned, separate paroxysms become more or less complicated or merged one with another, so that at first but slight transient intermissions, then perhaps only irregular remissions, and finally a continued fever of some height, result, the diagnosis becomes often more difficult. Such a case often presents itself in the form termed by Bacelli "subcontinua Typhoidea". The general clinical appearances are so similar to those of typhoid fever that a distinction without examination of the blood may be quite impossible. In a certain number of instances vestiges of the paroxysms still may be

made out, a well-marked acme in the fever being reached at approximately the same hour at quotidian or tertian intervals, though in other instances all traces of the individual paroxysms may have disappeared. Sometimes the history of several sharply intermittent paroxysms in the beginning of the illness may lead us to a correct diagnosis. Again, the prodromal symptoms are much less frequent and severe, as a rule, in malaria than in typhoid. Herpes is common in aestivo-autumnal malaria, unusual in typhoid fever. Delirium may appear quite early in a malarial attack: it is rare during the first few days of a typhoid. Bronchitis is more common in typhoid than in continued malarial fever. Marked abdominal symptoms, though they may occur, are unusual in malaria; the rule in typhoid. Certain erythemata - and especially urticaria - may be present in malarial fever, while the characteristic typhoid roseola does not occur. In both instances the spleen is usually enlarged. An important diagnostic sign is the anaemia which is almost invariably present if the malarial fever has lasted for more than a few days, while in typhoid fever anaemia during the first two weeks is rare. In typhoid fever Ehrlich's diazo reaction is almost invariably present, while it is not usually found in the urine of malarial patients. Another important sign is the slight icteric hue which is usually present in malaria, but rarely so in typhoid fever. The examination of the blood here, however, as in all forms of malarial fever will clear up any doubt existing; for the small, amoeboid, and ring-shaped, hyaline aestivo-autumnal parasites will be found. If the process has lasted a week or more, the pigmented and ovoid and crescentic bodies are also usually present. In rare instances quite severe febrile symptoms may be present, while the peripheral circulation may at times show but a small number of parasites. Here the discovery of pigment-bearing leucocytes may often be of assistance. The diminished number of leucocytes which one finds under these circumstances does not help us in the differential diagnosis from typhoid fever, where also the leucocytes are almost invariably subnormal in number. If the case occur in a neighbourhood where it is impossible to obtain the aid of the microscope, the diagnosis may be definitely made by the therapeutic test. No malarial fever no known resists good doses of quinine for more than three or four days. In general, if the process be malarial the temperature will be practically normal by the fourth day. The process is either non-malarial or a mixed infection if the drug fails to influence the fever.

The examination of the blood will also serve to distinguish malaria from typhus fever; and the same is the case likewise with tuberculosis or other septic infections.

PERNICIOUS MALARIAL FEVERS.

It is not always easy to effect a correct diagnosis in some of the pernicious forms of malaria.

Comatose pernicious fever must be distinguished from sunstroke, uraemia, and cerebral haemorrhage. The differentiation of such an attack from sunstroke is by no means simple. Individuals who are subjected to malarial infection are often those working in the fields and most exposed to the rays of the sun at the hottest

season of the year, while the clinical symptoms of the two processes may be closely similar. It is interesting to note that some of the cases recorded of comatose pernicious fever, occurring in tertian infection, were at first mistaken for sunstroke. The slight jaundice, the anaemia, the enlarged spleen would serve to suggest the malarial nature of the process, while the examination of the blood gives a positive clue to the diagnosis. The same also obtains in the case of the tetanic, the meningeal, the eclamptic, and the hemiplegic types of the disease. In the case of the algid type of paroxysm, where the temperature may be normal or subnormal, and where often - from the actual condensation of the blood - the anaemia may not be as apparent, the diagnosis may be considerably in doubt. Here, however, icterus and splenic enlargement are suggestive, while examination of the blood - which must never be neglected in any case - will give positive diagnosis. The diagnosis in some of the instances of the haemorrhagic type must be made between malaria and yellow fever. The spleen is often but little enlarged in this affection; and the early appearance of albumin and casts in yellow fever is suggestive of the nature of the disease. The only relaible method of distinction, however, is the examination of the blood. The diagnosis in malarial haemoglobinuria lies usually between yellow fever, the ordinary paroxysmal haemoglobinuria, and acute nephritis from some other toxic origin. Examination of the blood must here again be relied upon for a positive diagnosis. A diagnosis of post-partum and post-operative malaria can only be made by an examination of the blood. The blood, apart from the presence of the specific parasites and pigment, shows in the one instance diminution in the number of leucocytes, and well-marked leucocytosis in the other. Furthermore, the malarial paroxysms differ from the paroxysm due to septic infection chiefly by their greater regularity and by their average longer duration. It is usually a comparatively easy matter to diagnose chronic malarial cachexia. It is chiefly to be confounded with grave primary or secondary anaemia, or with leukaemia and pseudo-leukaemia. The malarial process may usually be distinguished from splenic anaemia by the presence of pigment and parasites in the blood. In some instances, however, where these are not to be found, the enlarged spleen, the grave anaemia, the haemorrhagic tendency, and the dropsical effusions present in both conditions may render the diagnosis almost impossible without appealing to the history of the patient. The progress of such cases is usually, however, decisive. The malarial cachexia responds, generally, slowly but progressively, to treatment. Thus one may see a spleen which reaches beyond the umbilicus, and almost to the pubes, diminish under treatment until it is only just palpable, while the blood returns to the normal condition as regards the number of its corpuscluar elements. Examination of the blood will also allow of a diagnosis from leukaemia. It is impossible to effect an absolute differential diagnosis between post-malarial anaemia and some other secondary anaemias. The tendency, however, in the post-malarial anaemia to a diminution in the number of leucocytes is always marked,

while a relative increase in the large mononuclear elements is very suggestive.Post-malarial nephritis has no special characteristics to distinguish it.

MIXED INFECTIONS AND OTHER COMPLICATIONS.

A certain diagnosis can only be made in some of the mixed infections already referred to by the discovery of the parasites,and the persistence of the complicating process after the disappearance of the organisms under the administration of quinine.Thus,a persistence of the characteristic symptoms after the clearing up of the complicating malarial process would allow of a diagnosis of typhoid fever.The usual well-known symptoms will serve to distinguish acute rheumatism, tonsillitis,paratitis,and the exanthemata from malarial fever.The diagnosis depends in the case of pneumonia more upon the physical examination,as it is well known that the malarial parasite in incapable of producing actual consolidation of the lungs.Pleurisy is also recognised by its classical physical signs and subjective symptoms.The malarial poison may or may not be directly responsible for the occurrence of diarrhoea or dysentery during the active malarial process.The presence of the Amoeba coli in the stools is evidence of a complicating process;while in other cases a postive diagnosis cannot be made until a response to quinine is observed in connection with diarrhoea in acute malaria.

PROGNOSIS.

So far as the probable outcome of the illness is concerned, the prognosis in tertian and quartan fevers is almost invariably favourable. It is only very exceptionably that one sees a case in which actual pernicious symptoms are present in tertian and quartan ague. Without systematic and cafeful treatment relapses and grave cachexia may, however, follow - a cachexia which may well lay the patient open to the gravest secondary complicating diseases. It is not improbable that repeated malarial infections in these cases may be followed by a fatal chronic nephritis. The prognosis is perfectly good in ordinary cases of aestivo-autumnal fever which come early under treatment. The latter must, however, be more active and longer carried out than in the regularly intermittent fevers. Cachexia and grave post-malarial anaemia are more likely to follow upon imperfectly treated cases. The prognosis is extremely grave, and, unless active treatment be instituted, usually wholly unfavourable in all cases in which pernicious symptoms have developed. On the other hand, however, the prognosis is usually favourable if active treatment has been begun during a pernicious paroxysm and no succeeding paroxysm has occurred within forty-eight hours. In a patient first coming under observation in a pernicious paroxysm an entirely favourable prognosis can never be given for at least fifty-eight hours after the beginning of treatment. It is always possible that a single pernicious paroxysm may be succeeded, despite treatment, by another upon the following day. The prognosis is always extremely grave in malarial haemoglobinuria: indeed, the dangers of a fatal outcome are not past until the disappearance of the urinary symptoms and of the fever. If the patient can be persuaded to remove to a more healthy locality, in the more severe grades recovery is extremely slow, and at times almost impossible; in the milder grades of chronic malarial cachexia, however, the prognosis is good is the patient can be made to adopt a preporly hygienic life. Of an extremely grave character are often the anaemias following malarial fever. The prognosis is almost as bad as it could possibly be in those cases where the blood shows the characteristics of true pernicious anaemia, and in those instances in which the nucleated red corpuscles are scanty or absent and the leucocytes are diminished in number. An unusually unfavourable course is apparently pursued by secondary infections occurring in individuals suffering from malarial cachexia; and the possible unfavourable effect of the coexisting malarial infection alone influences the prognosis in the various complications of malarial fever.

TREATMENT.

PROPHYLAXIS.

The greatest benefit is to be derived in malarial fever from prophylactic measures; and these belong in part to the domain of public hygiene, and in part fall within the scope of individual effort. Those dealing with proper drainage, cultivation of the soil, and so forth would require an article of even greater length than this for their consideration, so they cannot be described here. The individual mat adopt certain measures, however, which may protect him in the most malarious districts. If it be necessary to visit, temporarily, notoriously malarial districts, let him, so far as possible, choose the season of the year at which the fevers are least prevalent. The dwelling should be sought upon ground as high and as dry as possible. Exposure at night in damp or marshy districts should be avoided; the sleeping apartment should be upon an upper story of the house. Despite the experimental evidence that infection may occur through the gastro-intestinal tract, it is prudent to boil all drinking-water coming from malarious districts. Medicinally, quinine in small doses will often prove protective against infection. Monti has reported good results from the administration of the sulphate of quinine in doses of six grains every other day; but Sezary (Modern Medicine, 1892) says that under most circumstances even a little over two grains will be sufficient for the purpose. If the district be extremely malarious mthe various simple wines containing cinchona are insufficinet protection, and it is advisable to take several grains of quinine daily. The destruction of the mosquitos should be effected as far as possible; and the individual should protect himself from their bites in the usual way. Various sera have been manufactured for protecting the individual against the disease; but they are all at present of more or less doubtful efficacy.

MANAGEMENT OF THE DISEASE.

GENERAL MEASURES.

In the treatment of malarial fever there are certain general hygienic measures advisable, and sometimes very important. In all cases it is prudent to keep the patient in bed, if possible, for twenty-four or forty-eight hours: in the more severe aestivo-autumnal fevers it is absolutely necessary. The simpler regularly intermittent fevers often show a temporary and sometimes permanent spontaneous recovery following rest in bed, without further treatment. In hospital practice the patient should be kept in bed until the entire disappearance of the fever, whether it be intermittent or subcontinuous. The fact that the patients are so much more readily kept at rest may possibly account for the more satisfactory results of hospital treatment in malarial cases, in part at least. In the case of the patient being

resident in a very malarious district,it is always important,if possible,that he removed to more salubrious surroundings.Thus,recovery from chronic cachexia is greatly favoured by removal into higher and more healthy localities.In some instances of advanced cachexia the removal may be absolutely necessary.In the ordinary acute malarial fevers it is,however,generally peffectly possible to treat the case in the malarial district itself.The patient should be kept,while under treatment, in one of the upper stories of the house;he should be prevented from subsequent exposure to infection,if possible,and be warned against remaining out of doors at night during convalescence.The patient may be allowed an ordinary nourishing general diet in the simple intermittent fevers.During the paroxysms,which last but ten or twelve hours in all,the patient need not be forced to eat;it is,however,generally well that liquids,milk, broths,and soups should be taken in small quantities. Stimulants may be administered symptomatically.In the more severe subcontinuous fevers,where there is usually complete anorexia,the patient may be given liquids of all sorts,soups,milk,and broths,at short intervals; while,if he he be hungry and there be no gastro-intestinal disturbances,there is no contradistinction to soft solids and aggs.In cases where there are marked gastro-intestinal symptoms great care must,of course,be exercised with the diet;the diet should be entirely restricted to broths,boiled milk,albumin-water,and so forth. Exposure to the night air is held by the inhabitants of some malarious districts,and probably justly,to be injudicious:this observation is based upon experience. It may be unwise for the patient in such regions to be allowed to sleep with his window open.If,however,the patient be in a healthy district and be accustomed to living and sleeping with open windows,there is no reason why a change should be made during the existence of the fever.Provided the sufferer be accustomed to such air beforehand,there is no fever which we know of at present which is unfavourably influenced by fresh air and suitable ventilation of the sick-room.

QUININE.

This drug still occupies the front rank amongst all medicaments that have been advanced for the treatment of malarial fever:indeed,it is a real specific for that affection.Quinine,in the form of cinchona bark,was introduced into Europe,in 1640,by the countess del Cinchon,- wife of del Chincon,the Spanish governor of Peru,- who had recovered from a severe attack of intermittent fever after taking a powder administered by a corregidor of Loxa.So far as is known,this substance was first used by the Indians in America as a remedy against malarial fever.The powder,which was known at first as the "powder of the countess",and afterwards as the"Jesuits powder",- for the reason that it was introduced into general use by the Jesuits in Rome in 1649,- was prepared from the bark of a Peruvian tree.This was for years known as Perusian bark,though its officinal name,Cinchona,is derived from that of its introducer to the Eastern hemisphere.It was first administered in the form of the pulverised bark,the cinchona powder, which contains,in addition to various akkaloidal

substances, a considerable quantity of tannin. The various salts of its active principle, quinine, are now in use, and the pulverised bark abandoned.

The exact mode of action of quinine remained unknown for centuries after its introduction and after its specific effect in malarial fever has been discovered. As far back as 1867, Binz (Centralbl. f. d. med. Wiss., 1867, p.308) correctly concluded that the efficacy of quinine in paludism depended upon its action as a protoplasmic poison upon some lower organism which he assumed to be of the nature of the cause of the process. The extremely toxic action of quinine upon the infusoria was at that time clearly demonstrated. Since the development of our knowledge concerning the malarial parasite, it has been possible to study, to a certain extent, the direct action of quinine upon the haematozoa. Laveran noticed the immediate disappearance of the parasites following the administration of quinine, and in 1881 asserted that it is because it destroys the parasite that quinine causes the disappearance of the manifestations of paludism. He showed that by allowing a 1 : 10,000 solution of quinine to run under the coverglass the movements of the parasite were immediately arrested, as they are when any other protoplasmic poison is employed. The behaviour of the tertian and quartan parasites to quinine has been carefully investigated by Golgi. He observed that after the administration of quinine the quartan organism, in its endoglobular stage, shows a coarser granulation with a metallic reflex, while the protplasm shows a definite cloudiness. At times one may see abortive segmenting forms which are smaller than the normal, with a lack of regularity and fewer segments. The pigment also may not collect as sharply in a clump in the middle of the parasite. In the tertian parasite the changes are more marked, owing to the greater normal activity of the organism. The body is round and immovable, and shows a sharper outline than usual, while the pigment has a peculiar metallic reflex and tends to collect in clumps. Full grown tertian forms may present a large transparent swollen condition with very active movements of the pigment granules. Sometimes the pigment may collect towards the periphery, leaving a hyaline space in the middle. Mannaberg asserts that three hours after the administration of 0.5 of quinine the amœboid forms of the tertian parasite show a marked diminution of their activity. In several hours more the number has greatly diminished, while many of those present are fragmented, resulting in the presence of several separate spherules in the red corpuscle. Full grown forms show a cessation of the movements of the pigment, the body having a somewhat refractive homogeneous appearance. Large hydropic forms with active pigment may also be seen. These two latter forms may occur normally during the paroxysm, as Golgi and Mannaberg also assert; they are probably degenerative forms. In the case of the tertian parasite the somewhat greater refractiveness of the organism, the collection of the pigment into clumps, and the cessation of active movements, as well as the presence of a greater number of fragmenting forms, have been seen. Some very interesting studies with stained specimens have been made by Romanowsky (Cent. f. Bakt., 1892, xi, Nos. 6 and 7, 219; and St. Pet. med. Woch., 1891, Nos. 34 and 35)

and Mannaberg.Both observers noted the loss of affinity for colouring matters in the chromatin substance of the nucleus.They also observed that in the segmenting forms, after quinine had been given,the greater number of the segemnts show no nucleoli;and these changes in the nucleus they believed to be evidence of a necrotic process.The segments without nucleus Mannaberg termed "still-born".Marchiafava and Bignami ,studying the aestivo-autumnal fevers,note that the administration of quinine is followed by an increase in number of shrunken,brassy-coloured corpuscles.They believed that further development of the included parasites was impossible.Bacelli (Deut.med.Woch.,1892,No.32,721)noted that in aestivo-autumnal fever,after the intravenous injection of quinine,there was an increase in the activity of the small amoeboid forms,which,often inside of twenty-four hours,disappeared without showing any outward signs of degeneration.The vast majority of those who have been able to test the action of quinine upon the malarial parasite will agree with Golgi that in tertian and quartan fever quinine acts most markedly on the free young segments,less upon the more advanced forms where the red corpuscle is in greater part destroyed,and least upon the young endoglobular forms.If quinine be given several hours before the paroxysm,it will not prevent segmentation,but it will destroy the new group of parasites,the fresh segments.Segmentation takes place,toxic substances are produced and enter into the blood-stream,and the chill follows,being at most a little modified or retarded.The further development of the new group of organisms is,however,prevented, and on the following day no parasites whatever may be observed.The same appears to obtain in the case of the aestivo-autumnal parasite,the maximum and most rapid action of the remedy being exercised on that phase of the endoglobular life of the parasite which follows the completed segmentation.Golgi says that,in the case of the tertian and quartan organisms,the segmentation cannot be prevented if quinine be given when the parasite has reached the preparatory stages.The drug acts on the amoeba of malaria during those phases of its life in which it absorbs nourishment and develops; when the nutritive activity comes to an end,the transformation of haemoglobin into black pigment having been accomplished,and the phase of reproduction begins,then quinine becomes inefficacious against this process. Quinine should be in solution in the blood at the time of the setting free of the fresh parasites - i.e., during and several hours before the paroxysm - in order to best combat the further development of a group of malarial germs.In ordinary tertian or quartan fevers,with moderate regular daily does of quinine, the parasites will usually wholly disappear from the peripheral circulation inside of three days.In aestivo-autumnal fever the time may be a little longer.The crescentic bodies remain in the blood long after the disappearance of all other forms of the parasite,being affected slowly,if at all,with quinine.

Regarding the effects of the remedy upon the patient,in small doses,such as are ordinarily required therapeutically,quinine causes no subjective symptoms. In somewhat larger doses,however,it produces at times

a ringing in the ears, roaring or sometimes tinkling noises, and, finally, more or less deafness. Larger doses are followed by a dimming of the vision, even to complete blindness. Ringer has noticed that this may sometimes begin in one eye, and, indeed, exist for considerable time on one side only. The pupil is usually dilated. In larger doses a severe frontal headache, with giddiness and staggering gait, delirium, and great muscular weakness, may follow, and, finally, in still larger doses, convulsions and death. Sometimes larger doses of quinine are followed by certain cutaneous disturbances. Urticaria at times occurs; and Ringer describes an intense general erythema similar to a scarlet fever eruption and followed also by desquamation of the skin.

There is a proper method of administering quinine. Like another commonly used and extremely valuable drug, digitalis, quinine, which is our main-stay in malarial fever, is very frequently abused. Laveran well says: "In a general way it may be said that in malarial districts far too much sulphate of quinine is given to patients who have no need of it, while a sufficient quantity is not given to patients suffering from paludism". The very degree of its efficacy, as in the case of mercury and iodide of potassium in syphilis, is probably accountable for the lax manner in which it is frequently given. When one or two doses are followed by a complete disappearance of the symptoms, the immediate relief is so great that the patient fails to recognise the importance of continued treatment, and lays himself open to repeated relapses by abaddoning the regular régime. The determination of how and in what form quinine should be exhibited in any individual case is of considerable importance. The ordinary way of administration is by the mouth, and the common form in which it is given is as the sulphate. The sulphate of quinine is very slightly soluble in water, but quite readily soluble in dilute acids. The best manner to administer this form of quinine is in water containing a sufficient quantity of dilute hydrochloric acid, or sulphuric, to hold the salt in solution, it being customary to add one drop of the dilute acid to one grain of the salt. The extremely bitter taste is sometimes an objection in sensitive patients: this, in the case of the quinine powder, may be partly obviated by mixing with an equal quantity of powdered ginger. The drug may also be administered in the form of pills or in capsules. Quinine pills are convenient, but are open to the common objection that in many instances the commercial pill is a highly insoluble object. Thus, it is not at all infrequent in dispensary practice for the physician to be consulted by patients with simple intermittent fever who have taken quinine pills without effect, while the solution or the powder has an immediate result. For more rapid action the quinine may be administered hypodermically. The solution adapted for hypodermic injections is the following: Quinine hydrochlorate gr. 75, distilled water q.s. ad 3iiss. By using this solution we know that with a Pravaz syringe we inject 7½ grains of the salt. We can also use more dilute solutions, - e.g., 1 : 2 or 1 : 3, - in order to render the injection less injurious. The solution should be clear and the instrument and the skin of the part where the injection is to be given should be rendered aseptic. The injection

may be made in the back abdomen or gluteal region, in which situations some prefer to give it intramuscularly as being less painful or entirely painless. Strict asepsis will prevent the occurrence of tetanus, which in former times not infrequently made it appearance, following inflammation at the point of puncture, usually a few days after the injection. Although more or less troublesome subcutaneous indurations are sometimes unavoidable, severe eschars, abscesses, and even worse local injuries can be avoided by observing the precautions mentioned above. When prompt and energetic treatment is necessary, Bacelli suggests a method of intravenous injection of quinine. For this purpose more soluble salts than the sulphate must be used. The formula which he recommends is the following: Hydrochlorate of quinine, gr. xv.; chloride of sodium, about gr. xii.; distilled water, q.s. ad 3iiss. The solution must be perfectly clear, and should be tepid. Before giving the injection, a large bandage is bound above the elbow, as in the case of venesection, in order to swell the veins of the forearm; into one of these veins the needle is introduced, and then, the bandage having been removed, the fluid is slowly pushed in. A swelling at the point of injection is a sign that the needle has not been properly introduced into the vein. Bacelli says he has cured all his cases of pernicious fever in this way after twenty-four hours, there being no return of the pyrexia nor relapses. Others, however, do not speak so well of the method. After the needle has been withdrawn, the stab wound should be carefully closed with collodion. Another convenient way in which to administer the remedy is in the form of the bimuriate of quinine and urea, which contain nearly 80 per cent. of quinine and is soluble in less than its own bulk of water. It may also be given by the rectum; but quinine is seldom used in this way, except in the case of children and as a last resort. One may readily perceive the time at which - theoretically at least - the drug should be given, is we take into consideration the studies of Laveran, Golgi, Mannaberg, and others concerning the effect of quinine upon the parasite, and then remember the close relation between the development of the parasite and the symptoms of malarial infection. Inasmuch as it has been shown that quinine acts most effectually upon the young extracorpusclar parasite, it would seem fair to conclude that the period just before or during the paroxysm should be that at which quinine might be administered with most effect, and, as has been clearly shown, this is actually the case. A dose of quinine shortly before a paroxysm in the regularly intermittent fevers will not affect that paroxysm, but will prevent a recurrence of the succeeding one dependent upon that group of organisms. Thus, a single moderate dose of quinine, given just before or during a paroxysm in single tertian or quartan infection, will cause a general disappearance of the symptoms, while in the case of a double tertian infection it may often be seen to change the type of the fever from quotidian to tertian. Therefore, in such an instance the paroxysm expected upon the following day will occur, but that expected in forty-eight hours will not appear, the greater part of the group of parasites having been destroyed. Though the parasites are much more resistant to the action of quinine than those of the regularly intermittent fevers, the

same has been shown to be true in aestivo-autumnal fever. In the case of the regularly intermittent fevers it is generally advisable to place the patient upon regular treatment with quinine. If it be possible to keep the patient in bed, very small doses will often be sufficient. Thus, one grain three times a day will, in many instances, be followed by a disappearance of the symptoms. In practice we may give, according to the severity of the case, from two to five grains three times a day. If in tertian fever the patient be seen on the day before the paroxysms, five grains generally, three times a day, will, if the patient be confined to bed, prevent even any succedding paroxysm. One may predict, almost with certainty, the entire disappearance of the fever after this. If the patient be seen first just before an expected paroxysm or during the attack, it may be well to give a single dose (gr.v - x), and follow this by smaller doses (gr.ii) three times a day. If the paroxysms have been severe, it is sometimes wise to give large doses of the drug (gr.v - x) during the first days of treatment at the hour when without treatment the paroxysm might have been expected. Treatment with small doses (gr.vi), in twenty-four hours should be continued for at least three weeks, although the parasites in tertian and quartan infections disappear from the blood generally within three days. As a rule, larger quantities of quinine must be given for the treatment of aestivo-autumnal fever. In ordinary cases where no pernicious symptoms have developed, one may start treatment with five grains every four hours. In most cases under such treatment fever will entirely disappear inside of three days. If symptoms of cinchonism develop, the dose may be reduced. If the patient come under observation during a paroxysm, or if the history be obtained of a severe paroxysm having recently occurred, it may be well to begin with larger single doses. Thus, during or just before, a paroxysm ten grains may be administered, followed by five grains every four hours. If severe nervous manifestations accompany the paroxysm and the development of pernicious symptoms be feared, it may be well to administer the quinine hypodermically or intravenously. It is rarely necessary to give larger doses than fifteen grains. It may rarely be necessary to give several doses of this size at intervals of several hours during a long-continued paroxysm; usually two or three doses at intervals of four hours are sufficient, while afterwards it will be possible to give smaller quantities (gr.v) every four hours. Such doses will usually prevent the recurrence of a paroxysm due to this group of parasites. It is, however, possible that a second large group of parasites, which all treatment has failed to influence, may on the following day produce a fatal paroxysm. The same course should be pursued during the succeeding paroxysm. It has long been a well-recognised fact that if the patient survive the second paroxysm after the beginning of treatment, ultimate recovery is usually assured. In true pernicious paroxysms the experience of Bacelli would seem to show that the intravenous injections of quinine are by far the most efficacious. In the case of malarial haemoglobinuria, the same general rules which apply to the treatment of other pernicious fevers hold good. It should, however, be noted that certain observers believe that large

doses of quinine exert a distinctly injurious influence upon the blood, aggravating often the destruction of the red corpuscles. The view of Plehn is not generally accepted by the majority of clinicians; in a special article he goes so far as to advise an expectant treatment in these cases, asserting that recovery is more likely to result under careful nursing and general treatment than under the administration of quinine. There are various other cinchona derivatives that have been advanced as substitutes for quinine in the treatment of malarial fever; but their efficacy, however, is so far below that of the various salts of quinine that it is scarcely advisable to exhibit them. Thus, cinchonin, cinchonidin, quinidin, and quinoidin have been recommended. Finally, we must note that there are certain contra-indications to the use of quinine; the susceptibility to the drug varies greatly in different individuals. Relatively small doses produce cinchonism in some persons, while others are extremely tolerant of the drug. In the majority of instances, however, in which complaint is made it is based upon the fact that the drug has been administered in injudiciously large doses. Indeed, it is very seldom that one comes across a case in which it is impossible to administer quinine in sufficient doses to combat ordinary malarial manifestations without serious symptoms. Cases of this nature are extremely rare, and there are few instances probably in which individual susceptibility is any true contraindication to the administration of quinine in malarial fever. It is sometimes advisable to exhibit the drug in a form unfamiliar to the patient, for the prejudice against the remedy is very strong in the mind of some individuals.

METHYLENE BLUE.

By some methylene blue is said to be the most valuable remedy next to quinine in malarial fever. It was first employed, in 1891, by Guttmann and Ehrlich (Berl. klin. Woch., 1891), who were led to its use by the observation of Celli and Guarnieri that the malarial parasites were stained while yet living by this substance. They found that in small doses quite a marked effect was obtained in several cases of intermittent fever. Since this time the drug has been used by a number of observers, most of whom agree in the conclusion that methylene blue possesses a well-marked antimalarial action, the parasites often disappearing from the blood and the patient recovering after its administration. As an antimalarial agent it is, however, far below quinine in efficiency, while the parasite acquires, apparently, a certain tolerance to the drug after its continued use. In certain mild cases of the regularly intermittent fevers it may be given in doses of two grains every four hours in capsule, with possibly a curative effect. Larger doses have been given without ill effect - doses as high as forty-five grains in the twenty-four hours. The only unpleasant symptom following its use is, apparently, stranguary, which may be prevented by the administration of small quantities of powdered nutmeg at the same time. After the ingestion of methylene blue the urine has a deep blue colour, and the faeces become blue on exposure to the air. It is a remedy vastly inferior to quinine in this disease, and many observers have reported anything but satisfactory results from its administration.

PHENOCOLL.

This is an aromatic body, and a derivative of phenacetine. The hydrochlorate or acetate has been much used by the Italian observers for the treatment of malarial fever, especially in the case of children, but with only moderate success. It may be given in doses of ten grains.

OTHER MEDICAMENTS.

The treatment of malarial fever has been from time to time attempted by other drugs than those named above. Thus, iodine, strychnine, sulphur, arsenic, alum, preparations of eucalyptus and helianthus have been recommended. The value of these drugs, however, is slight, except, as will presently be mentioned, in the case of arsenic, which is often of service in anaemia and chronic malarial cachexia.

SYMPTOMATIC TREATMENT.

It is often advisable to supplement the treatment with the specific remedy by certain accessory and symptomatic measures. The value of purgation has long been insisted upon; and the old custom of beginning the treatment of malarial fever by administering a mercurial purge is still believed in by some, though in light cases of the disease it may be well where there are symptoms of gastric trouble to administer a laxative, at the same time regulating the diet according to indications. In cases where there are grave intestinal symptoms purgation must be avoided. Profuse vomiting or purging during a paroxysm should be controlled, ~~as far as possible, by morphia administered hypodermically~~. Excitement and active delirium during the fever may also at times require the use of bromides. Cold sponging or the actual cold bath may be of service in continued high fever, especially if delirium be present. In the collapse in pernicious fevers most active stimulation must at times be resorted to: alcohol, strychnine, and ether may be freely administered hypodermically. In the algid forms external heat should be applied, as well as enemata of warm water.

TREATMENT DURING CONVALESCENCE.

It is the anaemia that is the most serious symptom that may require treatment during convalescence. In these cases iron and arsenic are our mainstays. In most instances iron alone, either in the form of Blaud's pill or as the tincture of the perchloride, in full doses, will be followed by good results. In severe cases arsenic may be resorted to: it is best given in the form of Fowler's solution. It is well to begin with small doses - m.iii - three times daily, and to increase the dose steadily, one drop every other day, until the physiological effect is observed - slight suffusion and injection of the conjunctivae, gastro-intestinal symptoms, etc. The dose should then, after a few days' cessation, be reduced and maintained at the highest possible limit. Some very grave anaemias which closely resemble true pernicious anaemia, and react but little to iron, may show marked improvement after vigorous treatment with arsenic. It should be borne in mind that in rare cases arsenical neuritis may arise. Convalescence is frequently hastened by the exhibition of strychnine and bitter medicaments.

TREATMENT OF MALARIAL CACHEXIA.

It is often a very difficult matter to treat chronic malarial cachexia. Active treatment by quinine

will readily remove the parasite from the circulation and put an end to acute symptoms,but the extreme debility and the grave anaemia are often very obstinate. Owing to the great susceptibility of such patients to fresh injections or to a reappearance of an old infection after the cessation of treatment by quinine, it is sometimes almost necessary to remove the sufferer to a non-malarious district.The anaemia,which is usually the gravest symptom,should be treated according to the suggestions given above.It is in these cases that persistent treatment by arsenic is especially valuable. The majority of cases of malarial cachexia owe their origin to the carelessness of the patient,who fails to observe the ordinary prophylactic measures and does not carry out the proper treatment with quinine.The patient should be kept from all undue exertion: if the anaemia be very grave,rest in bed is important.The diet should be most nourishing,and the patient should be allowed to sit in the sun and fresh air in the middle of the day if the climate be not too hot.Bitter tonics are often valuable,particularly strychnine.Most of the cases of this nature will recover,even in a malarious district,if treatment be properly carried out.

Cold Quinine Notes 1st

The Management of the Children

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